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Edited by Frank E. Hytten

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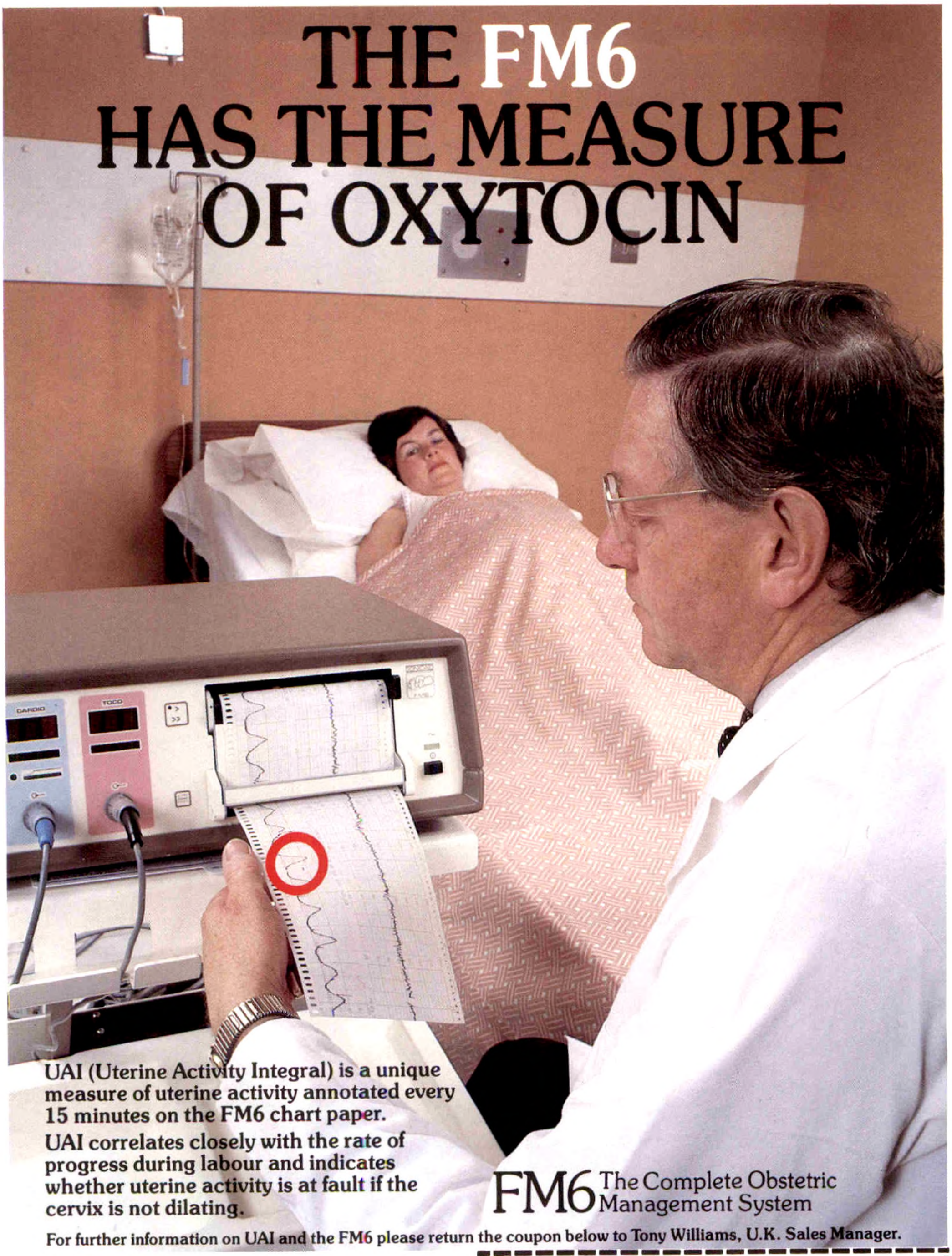

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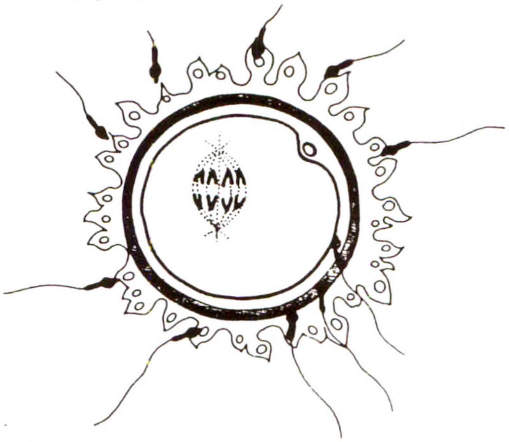

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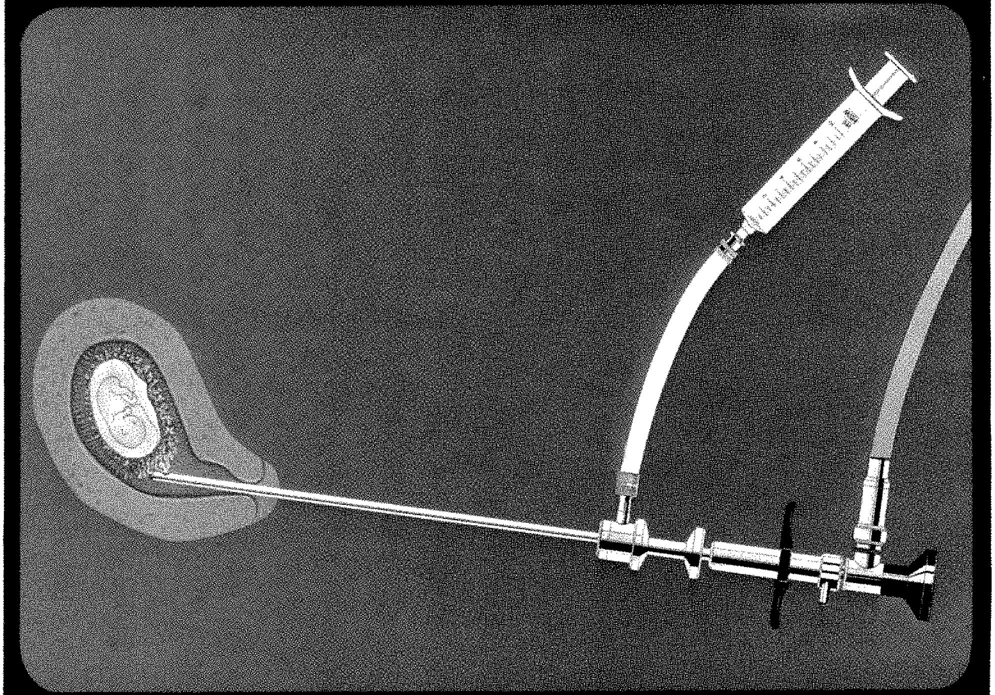

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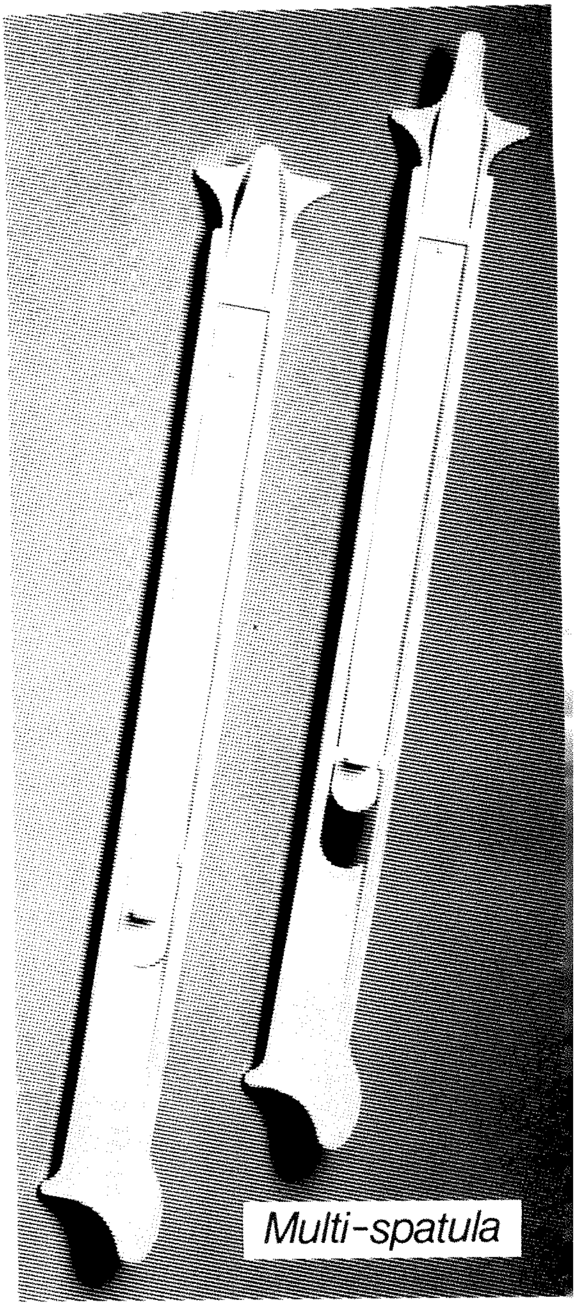

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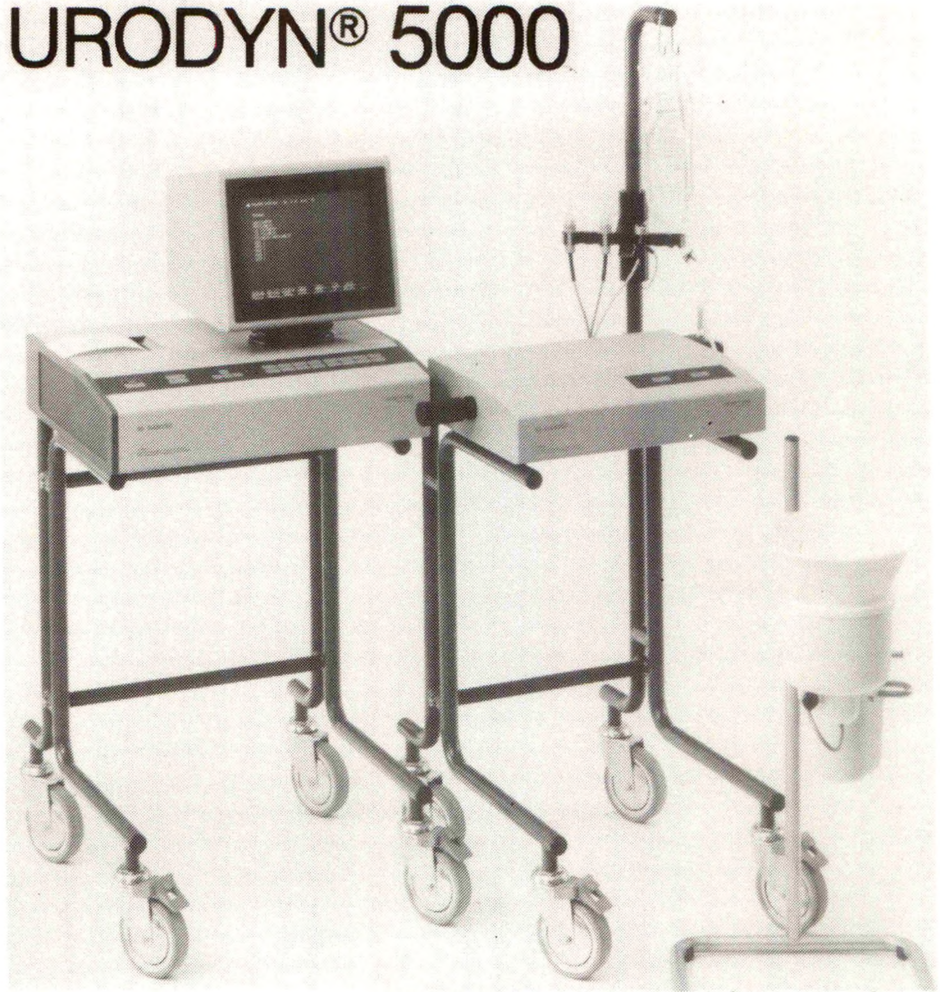

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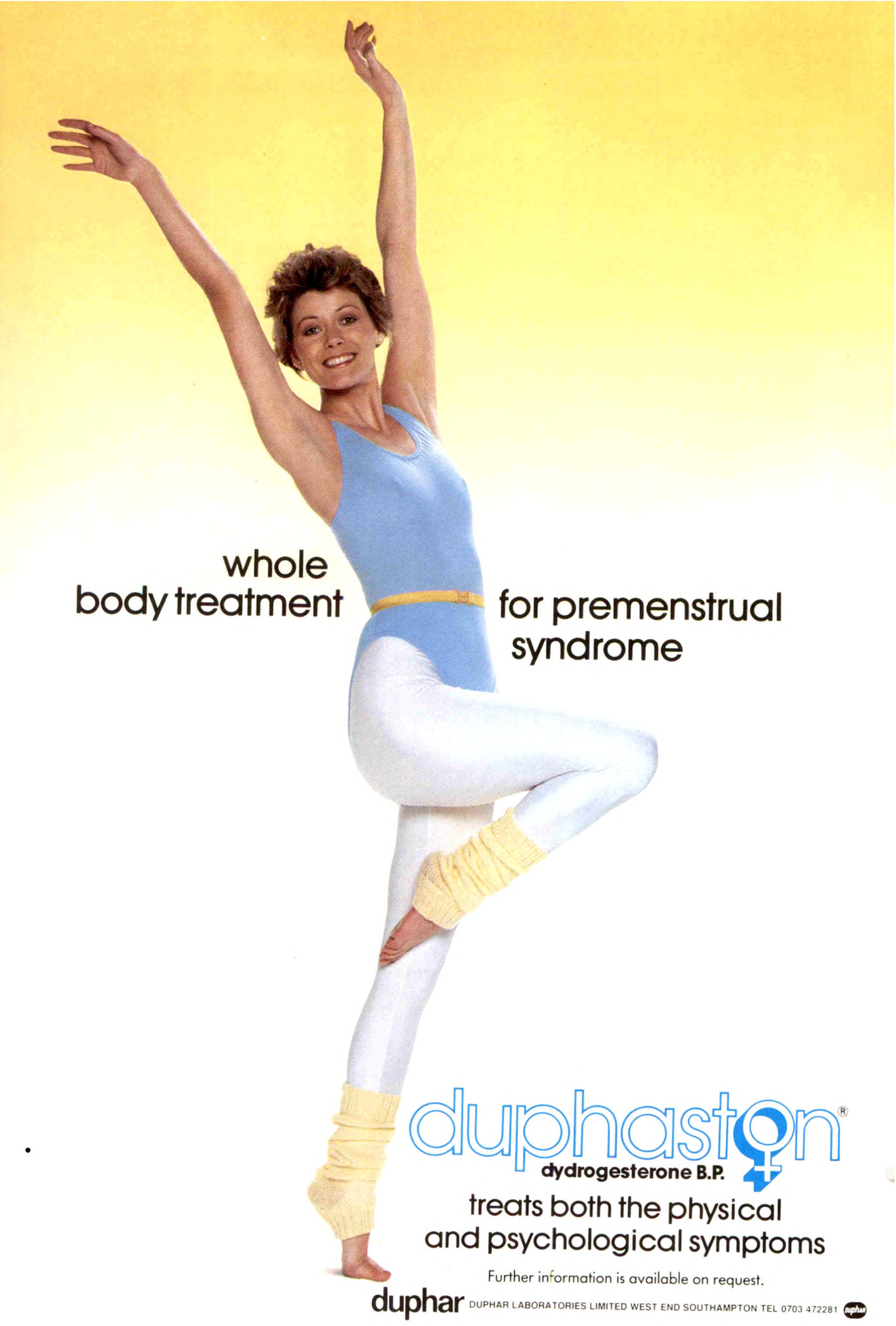

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British Journal of Obstetrics and Gynaecology
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COMMENTARY

The place of birth

The debate about the choice of place of delivery continues unabated as can be seen in four articles in this issue (pp. 659, 675, 684 and 690). Sadly the protagonists have tended to take up fixed positions, and the initially stimulating and useful discussion is in danger of degenerating into a sterile argument. It is perhaps a good time to look again at the questions which have been raised to see whether we cannot advance further.

To start, a reading of the literature suggests that there is often confusion between three separate issues. First, is home delivery more or less safe than institutional delivery, all other factors being equal? Second, is it inevitable that the rate of obstetric intervention must rise with the proportion of deliveries in consultant units? Third, what are the effects on mothers and babies of such a rise? Moreover there is a fourth issue, which is less well documented but also important, and that is the cost, in financial and manpower resources, of altering again the proportions of deliveries at home, in general practitioner and in consultant units.

It is now almost impossible to answer the first question about the relative safety of home and hospital confinements, and the reasons for this are well set out in the article by Campbell & Macfarlane (p. 675). However, all the available evidence suggests that in carefully selected and well-supervised low-risk deliveries the extra risk to mother and baby attributable only to the absence of hospital facilities must be low, and the satisfaction of a successful delivery high. Against this must be set the chance of needing an emergency transfer during, or after, the delivery, and although data on such events are limited, extrapolation from the experience of general practitioner units suggests it may be of the order of 10%, similar to the figures quoted by Scherjon (p. 684). Such emergency transfers are both distressing and costly if flying squad aid is needed, but it should not be forgotten that they may also occur in split-site hospitals where the maternity unit is removed from other specialist facilities.

The tendency for intervention rates to rise with the proportion of institutional deliveries is shown again in the paper by Scherjon (p. 684). A change in policy in Denmark between 1960 and 1980 led to a rise in institutional deliveries from 50% to 99%. During the same period this proportion in The Netherlands rose from about 28% to 67%. The caesarean section rate in both countries was about 2% at the beginning of the period, but rose to 11% in Denmark and only to 4% in the Netherlands. However, the wide variations found in intervention rates between institutions and countries suggests that this trend could be contained or reversed. Apart from the threat of litigation, we know very little about the factors which predispose to unduly high intervention rates, and this would be an interesting area of research. It would also be important to know, where there is a real choice between domiciliary and institutional delivery, how a woman's choice is influenced by her knowledge of the risk of possibly unnecessary intervention. For instance it is a pity that the paper by Treffers & Laan (p. 690), which shows remarkable differences in the proportion of domiciliary births between large cities in the Netherlands, did not also give us some indication of the variation in the rates of caesarean section, or other instrumental deliveries in the institutions in these cities.

The question of the benefits and hazards of these interventions in low-risk pregnancies is still largely unanswered. Campbell & Macfarlane (p. 675) show how even the ingenuity of Tew (p. 659) in manipulating published data on place of delivery and perinatal mortality cannot overcome the shortcomings of the data set. The same is true of Treffers & Laan's attempt to relate regional variations in the proportion of institutional births to the perinatal mortality rate, and Scherjon's comparison between such trends in The Netherlands and Denmark.

Major problems in such exercises are the impossibility of allowing sufficiently for the selection biases in women delivered in different places, and the inclusion of antepartum deaths and lethal congenital defects which are not affected by intrapartum care. It is time that such analyses were abandoned, and efforts channelled either towards randomized trials of specific interventions where these are still possible, or towards understanding the motivation for apparently unduly high levels of such interventions. The fear of litigation cannot affect the prevalence of epidural analgesia or of episiotomy.

Finally a most interesting aspect of Scherjon's paper is the discussion of the reasons for a planned policy change towards institutional delivery. In Denmark, as in the UK, this was originally on grounds of safety, because of inability to predict reliably the risk of complications to mother and child, and of course occurred when perinatal mortality risks were very much higher than they are now. Nevertheless, questions of cost and manpower also arise, and as Scherjon's paper suggests will vary with the actual proportion of institutional delivery.

In particular we lack careful studies of the numbers of midwives needed to provide a safe domiciliary service and the implications on their hours and work pattern of providing continuity of care. It may be that the price to be paid for a sizeable and safe domiciliary midwifery service is now too steep to be considered, bearing in mind also the needs of high-risk pregnancies in hospitals, but if this is so it underlines the need for hospitals to make available the type of low technology care that so many of their clients prefer.

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Do obstetric intranatal interventions make birth safer?

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Summary. Impartial analyses of the evidence from official statistics, national surveys and specific studies consistently find that perinatal mortality is much higher when obstetric intranatal interventions are used, as in consultant hospitals, than when they are little used, as in unattached general practitioner maternity units and at home. The conclusion holds even after allowance has been made for the higher predelivery risk status of hospital births as a result of the booking and transfer policies. It holds even more strongly for births at high than at low predicted risk. It follows that the increased use of interventions, implied by increased hospitalization, could not have been the cause of the decline in the national perinatal mortality rate over the last 50 years and analysis of results by different methods confirms that the latter would have declined more in the absence of the former. Data are presented which point to the deleterious effect of interventions on the incidence of low birthweight and short gestation and their associated mortality. Also presented are data supporting the alternative explanation of the decline in perinatal mortality, namely the improvement in the health status of mothers built up over several generations. The organization of the maternity service stands indicted by the evidence. Despite the beliefs of those responsible, it has not promoted, and cannot promote, the objective of reducing perinatal mortality.

Obstetric intranatal interventions have been developed with the objective of making birth safer and less painful, at least for the mother. The specific procedures were not subjected in advance to randomized control trials to prove that they would be advantageous in the circumstances in which they came to be widely used. Nor were the possible interactions between procedures investigated. In the absence of valid prior confirmation, their net benefit has to be judged from results—from comparing mortality rates following deliveries where they have and have not been used. However, it has not been thought necessary to record and publish results in a form that would make such direct comparisons possible. Nevertheless, enough information can be extracted from available data to make reliable evaluations of obstetric intranatal interventions as a whole and of certain specific interventions.

Certain interventions can be practised only in consultant hospitals and others are practised there far more often than in general practitioner maternity units (GPU) and at home, where most of the non-hospital births take place. Not all deliveries in hospital suffer intervention, sometimes because of the judgment of individual obstetricians, sometimes because birth follows too soon after the woman's arrival in hospital.

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Nevertheless, though they are an underestimate, the mortality rates in hospital can be taken as the nearest available proxy for the results of obstetric intranatal management as a whole.

The mortality rates in unattached GPU and home represent the nearest available proxy for the results of low interventive midwifery care, through they are an overestimate since births at home include some which have no professional care, either because they take place too quickly or because the woman has chosen not to have it. The sub-groups particularly affected by the latter reason include the very young and the unmarried. The mortality rate is many times higher when births take place without normal midwifery care (Tew 1981; Murphy *et al* 1984; Campbell *et al.* 1984). The effect on the home mortality rate of changes in the proportion such births make up of all home births will be considered later (Appendix 1).

The longest series of data linking mortality to these separate places of birth is to be found in the official stillbirth statistics 1969–1981, published annually by the Office of Population Census and Surveys (OPCS). But a simple comparison between the crude stillbirth rates (SBR) at each place may be misleading: to find out to what extent this is so requires first an understanding of the arithmetical rules governing the SBR, which are, of course, only a specific example of all mortality rates or other weighted averages.

Applied arithmetic

Stillbirth rates

The SBR per 1000 births is, of course, the number of stillbirths divided by the number of births in the same place and period, with the result multiplied by 1000. But it is also an average of the SBR in the component sub-groups, weighted by the proportion that each sub-group makes up of the total. This is demonstrated in Table 1A, using the official figures for 1969 (the first year available), which are cross-classified by age and parity. For simplicity of exposition let us assume only two sub-groups, a lower risk group consisting of second and third births to women aged 20–29 and a higher risk group including all the others. (Births in private hospitals and 'elsewhere', which made up 1·3% of all births, have been excluded.)

The overall SBR per 1000 births was 13·3, the weighted average of the SBR in hospital, 16·6, where 71·6% of births took place and in GPU/home, 4·9, with 28·4% of the births (16·6 × 0·716 + 4·9 × 0·284 = 13·3). The hospitals' SBR was much the higher, but so also was their proportion at higher risk (74% against 54%). Suppose as in Table 1B that each place had had the same proportion at higher risk (68%), the hospital SBR would have been slightly reduced and the GPU/home SBR slightly increased, but the margin between them would have remained wide. *It is arithmetically impossible that the margin could be closed or the disparity reversed as*

Table 1. Stillbirth rates per 1000 births (SBR), England and Wales 1969, showing how they depend on the proportion of births and the specific rate in sub-groups of risk*

	Total births (787 581 = 100%)			Hospital births (563 955 = 71·6%)			GPU/home births (233 626 = 28·4%)		
Risk group	Proportion of total	Specific rate	Product	Proportion of total	Specific rate	Product	Proportion of total	Specific rate	Product
A					Actual				
Lower	0·32	9·3	3·0	0·26	13·7	3·6	0·46	3·1	1·4
Higher	0·68	15·1	10·3	0·74	17·6	13·0	0·54	6·4	3·5
All	1·00	13·3	13·3	1·00	16·6	16·6	1·00	4·9	4·9
B		Actual			Hypothetical or standardized†				
Lower	0·32	9·3	3·0	0·32	13·7	4·4	0·32	3·1	1·0
Higher	0·68	15·1	10·3	0·68	17·6	12·0	0·68	6·4	4·4
All	1·00	13·3	13·3	1·00	16·4	16·4	1·00	5·4	5·4

* Source: OPCS (1971)
† By direct method

long as the specific SBR in hospital are higher in each sub-group. Clearly, the excess SBR in hospital in 1969 was to only a very small extent due to their excess proportion of births at higher risk on account of age and parity. It was predominantly due to the fact that for every sub-group distinguished in the statistics, the specific SBR was much higher in hospital; indeed, in the summary groups in Table 1, the SBR for the lower risk group in hospital (13·7) was more than twice as high as for the higher risk group in GPU/home (6·4).

A weighted average will be higher the greater the proportion it includes at high risk, and conversely. If over time proportions in sub-groups change, the weighted average must, in the absence of counteracting influences, change in the appropriate direction. As the policy towards 100% hospitalization was implemented, the proportion of planned deliveries at home was progressively reduced, leaving the uncared for deliveries, with their very high mortality rate, to make up an increasing proportion of the diminishing total. This caused the mortality rate at home to rise, the increase reflecting simply the increased proportion at high risk and not, as was too readily assumed (Russell 1981), increased danger from domiciliary midwifery. The 'hard core' of uncared for deliveries with overriding social problems has been independently estimated at around 2000 (Tew 1981; Murphy *et al.* 1984; Campbell *et al.* 1984). The arithmetical consequences of the changed proportions are illustrated with realistic values in Appendix 1.

In turn the mortality rate for the GPU and home combined has become increasingly an overestimate of the risks of low interventive intranatal care. At the same time hospital births have become progressively diluted with low risk cases which formerly would have been delivered in the GPU or home, a process which should have reduced hospital mortality. Nevertheless, the results for 1981 (Table 2), the last year available, show that disparities persist between the SBR in hospital and GPU/home, at specific levels and overall, with magnitudes highly unlikely to have happened by chance ($P<0{\cdot}001$). The lower risk group in hospital still had a higher SBR than the higher risk group in GPU/home. By 1981 hospital births included 95·4% of the total (non-NHS hospitals and 'elsewhere' again excluded). If this proportion had remained the same as it was in 1969 (71·6%), the SBR for all births would have fallen, not to 6·6 as it did, but to 5·9 ($0{\cdot}716 \times 6{\cdot}7 + 0{\cdot}284 \times 3{\cdot}8$). The increase in hospitalization, therefore, retarded rather than advanced the decline in the SBR. Other evidence supporting this conclusion and an alternative explanation for the reduced mortality will be considered later.

Perinatal surveys

The validity of analysis of SBR by age and parity is challenged on the grounds that these factors are only partially representative of all the risk factors which doctors take into consideration in selecting cases for hospital delivery and of the complications which develop in pregnancy or labour and lead to transfer from a GPU or home booking into hospital for delivery. Data gathered in the national perinatal surveys of 1958 and 1970, in which obstetricians were closely involved (Butler & Bonham 1963; Chamberlain *et al.* 1978), enable this challenge to be evaluated.

Table 2. Stillbirth rates per 1000 births, England and Wales 1981*

	Total births (630 512 = 100%)			Hospital births (601 741 = 95·4%)			GPU/home births (28 771 = 4·6%)		
Risk group	Proportion of total	Specific rate	Product	Proportion of total	Specific rate	Product	Proportion of total	Specific rate	Product
Lower	0·29	5·2	1·5	0·28	5·4	1·5	0·43	2·6	1·1
Higher	0·71	7·2	5·1	0·72	7·2	5·2	0·57	4·8	2 7
All	1·00	6·6	6·6	1·00	6·7	6·7	1 00	3·8	3 8

* Source· OPCS (1984)

Effect of the transfer policy on perinatal mortality rates (PNMR)

Women who were transferred had a very high PNMR and the conventional argument is that these should properly be attributed to the place of booking, not the place of actual delivery. This would be logical if the objective were to compare the total risk of *booking* for hospital with the total risk of *booking* for GPU or home, including the risk of transfer, taking the risks attendant on the different methods of intranatal care at each place as given. But it is not logical if the objective is the much more fundamental one pursued here of comparing the results of actual care by the different methods. It becomes fallacious to compare the results of obstetric care on the one hand with midwifery care plus obstetric care (the transfers) on the other. Obsession with comparisons by intended place of delivery has persistently obstructed efforts to evaluate the actual methods of intranatal care.

However, even if the fallacy were tolerated, comparison of results by place of booking could not reverse the excess mortality in hospital, overall or in specific sub-groups. In the 1958 survey the crude PNMR for actual deliveries was 50 in hospital, compared with 20 in GPU/home. The PNMR by place of booking was 36 in hospital, compared with 31 in GPU/home—still a highly significant difference ($P<0{\cdot}001$).

Corresponding data for the 1970 survey were not published but enough data were later supplied (J. Golding, personal communication) to enable an estimate of the extreme limiting case to be made. The crude PNMR for actual deliveries was 27·8 in hospital, compared with 4·9 in GPU/home [excluding GP beds in consultant hospitals where intranatal care may be considerably influenced by obstetric methods (Tew 1984)]. The PNMR in hospital for booked deliveries was 22·9, while for deliveries not booked or not known to be booked it was 58·9. On the extreme, and unlikely, assumption that all of the latter were transfers from an unattached GPU or home, then including these would raise the PNMR for all GPU/home bookings to 19·2, still lower than the 22·9 for hospital bookings. Thus in both surveys the excess PNMR in hospital could not be explained by the very high PNMR of the transfers or unbooked cases. It is highly probable that this applies also to the consistent excess SBR in hospital.

Table 3. Standardized perinatal mortality rate (PNMR) by risk factors*

PNMR per 1000 births	Hospital	GPU/home
Crude	27·8	4·9
Standardized for		
Age	27·5	5·2
Parity	27·3	5·1
Antenatal prediction score	26·6	5·4
Labour prediction score	23·9	7·7
Birthweight	22·9	9·6

* Source Chamberlain *et al* (1978) and unpublished data

Effect of the booking policy on the PNMR

Data from the surveys give even less support to the contention that the excess PNMR in hospital is the result of the booking policy. In the report of the 1958 survey, detailed data by place of delivery were given for only three risk factors known early enough to influence booking or a change of booking: parity, social class and toxaemia. Hospital births included a rather greater proportion in the higher grades of risk, but since their specific PNMR were higher at every identified grade, high and low, their excess overall PNMR could not have been explained by their greater proportion at higher risk. The same is true for the PNMR for hospital bookings, for their specific PNMR at every grade of risk was never lower than for GPU/home bookings, except for first births were it was marginally less.

In the report of the 1970 survey, specific PNMR by place of delivery were given only for hypertension and at every grade, including severe toxaemia, they were more than twice as high in hospital as in GPU/home. For age and parity, the proportion of births in each subgroup at each place was given, along with the specific PNMR for all places. This enables standardized PNMR to be calculated by the indirect method illustrated in Appendix 2 and these are presented in Table 3.

To meet the problem that some births are at high risk from more than one factor, two risk scores were constructed: an antenatal prediction score (APS) incorporating risk factors which are known early in pregnancy and influence booking, and a labour prediction score (LPS) incorporating also risk factors which develop up to and including the first stage of labour and which influence transfers These two scores provide more refined instruments by which the effects of the booking and transfer policies on the PNMR may be measured. The composition of the two scores is set out in Tables 4 and 5 and according to these tariffs an APS and an LPS was determined for every birth in the survey—a completely unbiased procedure.

The antenatal prediction score (APS)

While a maximum APS of 30 was possible, only 7% of births had scores over 8 (identified as the high risk group) and 53% had scores of 0–2, the low risk group. As expected, hospital births included a greater proportion at high and moderate risk, but the PNMR, standardized as in Appendix 2, show that very little of the hospitals' excess mortality was due to this excess risk; indeed very little more was due to the excess risk from the combined than from the single factors (Table 3). This reflects the interdependence of factors and makes it improbable that including additional factors in the APS, like height or smoking, would explain much more of the disparity.

Again, specific PNMR by APS were not published, but if they are estimated by simple algebra on the assumption that the ratio between the PNMR at each level of risk was everywhere the same, the PNMR in hospital are seen to be much the higher; as before the PNMR for the low risk group in hospital was much higher than for the high risk group in GPU/home (Table 6). Clearly, very little of the hospitals' excess PNMR arose from the booking policy.

The labour prediction score (LPS)

While a maximum LPS of 22 was possible for singleton births, the highest actual score was 12 and only 2·6% of births had scores over 6, while nearly 70% had scores of 0–2. The greatest risk was deemed to come from adverse conditions near delivery, but clearly these could have affected only a small minority of births, though they were more likely to affect women at high risk because of factors included in the APS. Births with the same LPS can be regarded as being at the same overall risk, so that groups with the same LPS can properly be compared. Groups of births in hospital, irrespective of how they came to be there or how the risk has developed, can properly be compared with groups in GPU/home with the same LPS at the same stage of labour. The LPS thus provides an instrument of analysis which obviates the problems of allowing for the selection biases of booking and transfer.

Results by LPS and place of delivery were not published, but the data were later released following a private request from the present author (J. Golding, personal communication). These show that, as expected, hospital births included a greater proportion at all scores over 2 (Table 7), but standardizing as before shows that this excess still explains only a small part of the hospital's excess PNMR (Table 3).

Again this is inevitable, for at every score from 0 to 8 the specific PNMR was higher, usually very much higher, in hospital The PNMR for the 90 (0·8%) births in hospital with

Table 4. Antenatal prediction score (APS). Weights given to risk factors*

	Risk		
Factor	Low	Moderate	High
Maternal			
Age	0	1	2
Parity	0	1	2
Social class	0	1	2
Obstetric history			
Stillbirth			4
Neonatal death			4
Abortion			4
Caesarean section			4
Hypertension			4
Diabetes			4

* Source: Chamberlain *et al* (1978).

Table 5. Labour prediction score (LPS), singleton pregnancies. Weights given to risk factors*

	Risk		
Factor	Low	Moderate	High
Antenatal prediction score	0	1	2
Previous caesarean section			4
Hypertension/toxaemia	0	1	2
Antepartum haemorrhage			2
Duration of pregnancy	0	1	2
Duration of 1st stage	0	1	2
Fetal distress	0	1	2 or 4
Breech presentation			4

* Source: Chamberlain *et al.* (1978).

Table 6. Proportion of births and estimated perinatal mortality rate (PNMR) by antenatal prediction score (APS)†

		Survey PNMR		Proportion of births		PNMR*	
APS	Risk	Actual	Ratio	Hospital	GPU/home	Hospital	GPU/home
0–2	Low	15·3	1·0	0·47	0·67	19·3	3·9
3–7	Moderate	25·9	1·69	0·44	0·30	32·6	6·5
8 and over	High	43·4	2·84	0·08	0·03	54·8	11·0
All		21·4		1·00	1·00	27·8	4·9

* For hospital: $(0{\cdot}47x) + (0{\cdot}44 \times 1{\cdot}69x) + (0{\cdot}08 \times 2{\cdot}84x) = 27{\cdot}8 \therefore x = 19{\cdot}3$.
For GPU/home: $(0{\cdot}67y) + (0{\cdot}3 \times 1{\cdot}69y) + (0{\cdot}03 \times 2{\cdot}84y) = 4{\cdot}9 \therefore y = 3{\cdot}9$.
† Source. Chamberlain *et al.* (1978)

Table 7. Percentage of births and PNMR by labour prediction score (LPS)†

		Percentage of births		PNMR	
LPS	Risk	Hospital	GPU/home	Hospital	GPU/home+
0–1	Very low	39·4	59·4	8·0	3·6*
2	Low	23·0	22·3	17·9	4·8**
3	Moderate	15·6	10·6	32·2	2·0***
4–6	High	13·2	7·5	53·2	14·2**
7–8	Very high	2·9	0·2	149·1	111·1
0–12	All	(n = 11141)	(n = 4660)	27·8	4·9

Level of significance: *$P<0{\cdot}025$, **$P<0{\cdot}005$; ***$P<0{\cdot}001$
+ Excluding GP beds in consultant hospitals
† Source: Unpublished data from the British Births 1970 survey.

scores of 9–12 was 211; one of the three births in GPU/home with a score of 9 died. But this is far too small a sample on which to base conclusions about the relative safety of the tiny proportion of highest risk births. The detailed data for scores 0–8 are summarized in Table 7.

The LPS is validated in that low scores are associated with a low PNMR and vice versa. But the association is less than perfect, for the lowest PNMR for hospital births occurred at LPS 1 and for GPU/home births at LPS 3. This may indicate that the relative weights given to the component factors are slightly unrepresentative of their true risk. Alternatively, it may simply be the artefact of small numbers. This is particularly likely in the GPU/home births, where there was only one death in 493 births at LPS 3. But the closeness of the PNMR in GPU/home over the LPS range 0 to 4 suggests that the method of intranatal care practised overcomes certain predicted risks, whereas the substantial increase in the PNMR among hospital births as the LPS increases suggests that obstetric management intensifies the risks.

These findings support the often expressed theory of Michel Odent that the fetus already at increased risk is less able to withstand the stresses of obstetric intervention. They confirm also, with greater authority, the invariable findings of higher stillbirth rates in hospital for the high risk age and parity groups as well as the low.

The findings could only be reversed if the mortal conditions of intrauterine death and congenital malformation, which are not specifically measured in the LPS and which are not influenced by intranatal care, were present in overwhelming excess among hospital births. But this possibility does not stand up to investigation. In the survey the early neonatal mortality rate in hospital was alone far higher than the perinatal mortality rate in GPU/home (Chamberlain *et al.* 1975), while in the year 1970, the SBR from congenital malformations was only 3% higher in hospital than in GPU/home (OPCS 1972).

An equally untenable hypothesis to explain the findings concerns the presence of other risk factors, recognized or unrecognized, not included in the LPS. If these were interdependent with the included factors, most of their effect would already have been allowed for. If they were independent, they would have to be much more powerful than the combined factors in the LPS to explain the outstanding disparity in PNMR. No such factors have yet been recognized far less measured. If they are unrecognized, there is no mechanism by which hospital births could come to include an overwhelming excess of them in the high-risk grades. Since maternal fear, stress and lack of self confidence militate against easy and successful labour, an excess of these factors could contribute to the excess of risk among hospital births, but this could arise only if the hospital environment in fact belies the reassuring promises of insistent antenatal propaganda that birth is safest under obstetricians' control.

If then only a small part of the excess PNMR of hospital births can be shown to be due to their excess of risk before delivery, the strong presumption must be that the rest is due to their excess of risk during or after delivery.

Complications and transfers

Complications similar to those that led to transfer must have occurred also among hospital booked cases. It had earlier been calculated (Tew 1984) from the data by place of birth and place of booking then available that if the incidence of complication was the same in both places, then the PNMR for the complicated cases in hospital must have been much higher than for the transfers; or that if the PNMR for the complicated cases in hospital was the same as for the transfers, then the incidence of complication must have been much greater in hospital, assuming in both cases that the incidence of and PNMR for cases without complication were the same in each place. Alternatively, if the incidence of complication and the associated PNMR were the same in both places, then the PNMR for births without the complications that led to transfer must have been much higher in hospital.

The data on specific PNMR by LPS now available confirm these inferences. At the LPS of 0 and 1, which were too low to include high-risk bookings or transfers because of complications, the PNMR was twice as high in hospital as in GPU/home. At higher LPS hospital births would include some transfers but many more booked births with similar complications, complications which must have been suffered also by births in GPU/home with the same LPS. Apparently booking for hospital, and the associated antenatal care, was less successful in preventing complications and the higher PNMR in hospital show that obstetric intranatal care was much less successful in mitigating their consequences than was care in GPU/home.

For the majority of cases transfer must have been disadvantageous: their PNMR would have been lower if they had remained in the GPU or home. This emphasizes how illogical, irrelevant and misleading it is to attribute their mortality to their place of booking, if the objective is to evaluate different methods of actual intranatal care.

In the 1958 survey, transfers represented 13% of GPU/home bookings and had a PNMR over six times as high as the PNMR for GPU/home deliveries. In the 1970 survey, on the extreme estimate made earlier, the incidence had risen to 26% and the excess mortality to nearly 12 times, though one would expect the greater percentage to include more cases with less serious complications and so to have a smaller excess PNMR. The reasons for transfer in pregnancy include most frequently toxaemia and post-maturity and much less frequently antepartum haemorrhage (APH), disproportion and malpresentation, while poor progress is the commonest reason for transfer in labour (Bull 1980). The PNMR associated with severe toxaemia was quantified in the 1970 survey as just over twice that associated with no toxaemia; the PNMR at >42 weeks gestation as just over twice that at 39–42 weeks, the PNMR associated with labours lasting >18 h as 1·2 times that with shorter labours; the PNMR associated with antepartum haemorrhage (APH) as less than four times that with no bleeding. If malpresentation, disproportion or the other conditions which lead to transfer result in caesarean section, then a PNMR about 2·5 times that for spontaneous cephalic presentation would be expected. Even if the other reasons for transfer carry a high mortality rate, they make up such a small proportion of all transfers that they raise the overall average only slightly. Thus the PNMR for a group made up of such high-risk cases who were transferred would hardly be expected to exceed the PNMR of a group, which included only a minority of high-risk cases who were not transferred, by more than a factor of 3, and certainly not by a factor of 6 (as in 1958), far less a factor of nearly 12 (as in 1970), unless the treatment following the transfer added greatly to the risk. Evidence from specific studies, when analysed, leads to the same conclusion (Tew 1985; Barron *et al.* 1977; Bull 1980). Between 1958 and 1970 the excess PNMR in hospital, overall and for transfers, increased greatly. So also did the practice of obstetric interventions; the induction rate, for example, increased from 13% to 26%.

Trends in interventions

Since 1970 the range of obstetric interventions has become ever more sophisticated and these have been applied to an increasing proportion of births as the percentage of all births in hospital has risen from 69·6 in 1969 to 94·2 in 1981. Over the same period the national PNMR has declined at an accelerating rate from 23·4 to 11·8. Like their predecessors the new interventions were not evaluated impartially before they were introduced and there has been no recent survey to assess their benefits, or otherwise, retrospectively. However, as has been shown in Table 2, the excess SBR in hospital still obtained in 1981 and the national SBR would then have been lower than it actually was if the proportion of births in hospital had not increased.

The same conclusion is reached if the proportional increases in hospitalization are correlated with the proportional decreases in the national PNMR in the corresponding years. A product moment correlation coefficient can be calculated from the pairs of proportional values; alternatively, the proportional values for hospitalization and PNMR can each be ranked and the ranks correlated. The results by each method are the same. The latter method is used in Table 8 and Fig. 1 from which it is clear that the years when hospitalization increased most were the years when the PNMR decreased least and vice versa. The correlation coefficient (Spearman's rho) is significantly negative ($-0{\cdot}87$, $P<0{\cdot}001$), which implies with a high degree of confidence that if hospitalization had increased proportionally less, the PNMR would have fallen proportionally more. Similarly, in Holland, and in Finland the decline in PNMR was not caused by increased hospitalization (Kloosterman 1978; Hemminki 1983).

Official maternity statistics enable similar calculations of correlations between the national PNMR and rates of induction, over the years 1964–1982, and forceps delivery and caesarean section, over the years 1962–1982, to be made. The pattern of these interventions over time has been different.

Induction

The percentage induction rate trebled from 13·4 in 1964 to 39·4 in 1974, remained around 37 till 1978, then nearly halved to 18·8 in 1982. Again, the larger proportional increases in the induction rate took place in the years when the proportional decreases in the PNMR were smaller,

Table 8. Trends in perinatal mortality and hospitalization, England and Wales*

	Perinatal mortality per 1000 births			Births in consultant hospitals		
Year	Actual	% change from year before	Rank of change	Rank of change	% change from year before	Percent of all births
1969	23·4					69·6
1970	23·5	+0·4	12	1½	+4 9	73·0
1971	22·3	−5·1	7	5	+3·6	75·6
1972	21·7	−2·7	11	4	+4·2	78·8
1973	21·0	−3 2	9	3	+4·4	82·3
1974	20·4	−2 9	10	1½	+4·9	86 3
1975	19·3	−5·4	5	6½	+1·8	87·9
1976	17·7	−8·3	4	12	+0·5	88·3
1977	17·0	−4 0	8	6½	+1·8	89 9
1978	15·5	−8·8	3	8	+1·4	91·2
1979	14·7	−5·2	6	9½	+1·2	92 3
1980	13·3	−9·5	2	9½	+1·2	93·4
1981	11·8	−11 3	1	11	+0 9	94·2

*Sources: Annual data published by the OPCS including Registrar General's Statistical Review, Birth Statistics and Mortality Statistics.

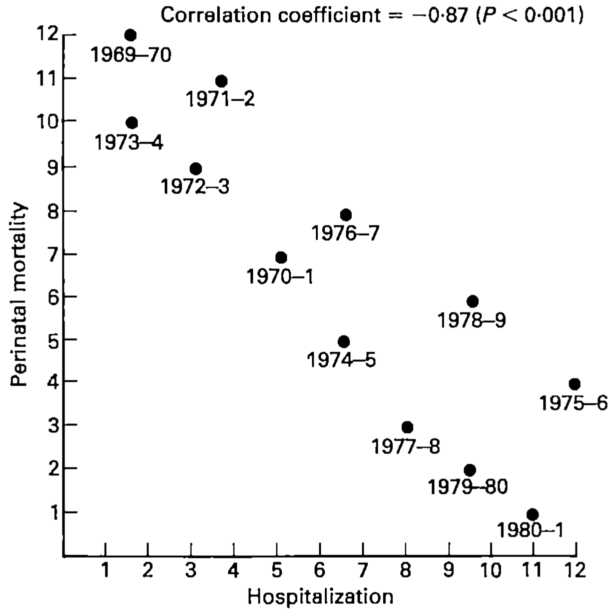

Fig. 1. Scattergram of ranks of proportional changes in rates of hospitalization and perinatal mortality. Rank 1 denotes the greatest increase in hospitalization and the greatest decrease in perinatal mortality. Rank 12 denotes the smallest increase in hospitalization and the only increase in perinatal mortality.

and vice versa, so that the rank correlation coefficient between the variables is significantly negative ($-0{\cdot}60$, $P<0{\cdot}01$). A lower induction rate would probably have led to lower mortality, but an optimal level could only be prescribed after evaluative studies. In 1982 there was wide regional variation in the rate—from 13·1% to 22·9%.

The principal medical indications for induction are post-maturity, suspected fetal growth retardation and certain maternal morbidity. Induction may be carried out also to suit the convenience of hospital staff or the mother, as the lower incidence of births at weekends and public holidays would seem to show (Macfarlane 1978). This last reason may have been relatively important in the 1970s when induction was carried out in nearly the same proportion of births without as of births with 'complication or anomaly' (OPCS Monitor 1981), and not much less often in births with the lowest antenatal prediction scores (Chamberlain *et al.* 1978). Apart from this hint, the official figures do not distinguish the contribution attributable to specific indications either before or after the abrupt decline in induction in 1978, so they do not reveal to what extent policy has changed in response to social pressure or to medical evidence.

Studies by obstetricians have found that the PNMR would not have been reduced by an induction rate above 9·5% (O'Driscoll *et al.* 1975) or 8% (Williams & Studd 1980). More specifically, a comparison of 30 induced and 51 spontaneous, post-mature labours, in women who were otherwise well-matched, led to the conclusion 'that a pregnancy prolonged after 42 confirmed weeks of gestation may affect perinatal outcome but induction of labour does not improve this and that uncomplicated post-maturity is not an indication for induction of labour' (Gibbs *et al.* 1982).

Corresponding evaluative studies of induction in relation to the other common indications do not seem to have been reported. There is as yet no method of reliably identifying growth retarded fetuses and intervention has resulted in the birth of many premature, but not growth retarded, infants (Hall *et al.* 1980). Nor has it been demonstrated that the truly growth retarded babies survive better if their gestation is curtailed or thrive better with intensive paediatric care than *in utero*. On the contrary, 'The reported incidence of major handicap, including cerebral palsy, in pre-term small-for-dates babies, followed up for at least 2 years, is much higher than in their term counterparts' (Chiswick 1985). One of the main justifications claimed for routine ultrasound scanning, the long-term consequences of which are unknown, is the precise dating of gestation, but this knowledge seems to be material only if induction or elective caesarean section is contemplated and proved, not simply assumed, to be beneficial for the specific indication.

There are biological reasons why induction of labour can lead to further interventions before birth (Inch 1982) and the official data show that the rates for certain procedures were indeed very significantly higher following induction (Table 9). However, the greater number of these actually carried out did not follow induction and most induced labours did not incur these particular further interventions.

Forceps delivery

The percentage rate of forceps delivery increased steadily from 8·1 in 1962 to 13·2 in 1977, then decreased to 10·3 in 1982. The need for forceps is dependent to some extent on induction but to a greater extent on other factors, including, for example, epidural analgesia (Hoult *et al.* 1977) which has greatly increased in use in recent years. However, this increased need must have been more than offset by reduced need from other factors since there has been a net decline in the rate. The rank correlation coefficient between proportional changes in the forceps rate and PNMR over 20 years is negative, but not significantly so (−0·30, $P<0{\cdot}10$). Nevertheless, the PNMR would probably be lower if forceps were used less often. In 1982 the average rate varied from 7·5% to 12·5% in different regions.

Caesarean section

The percentage caesarean section rate climbed slowly from 4·7 in 1962 to 5·3 in 1972 and then much faster to 10·1 in 1982. In this case the rank correlation coefficient over 20 years was positive though not significant (+0·36, $P<0{\cdot}10$). If the method of trend analysis used here results in a negative correlation coefficient between the variables, the existence of a positive causal relationship is at once effectively discredited. The finding of a positive correlation coefficient, however, is by itself inconclusive and more rigorous tests would be necessary to rule out the possibility that the trends in both variables simply reflect the influence of some other factor. Over the first 11 years the correlation coefficient was significantly positive (+0·61, $P<0{\cdot}05$), but since caesarean section affected only 5% of births it could have had only a marginal influence on the overall PNMR. Over the next 9 years, when caesarean section became increasingly frequent and could have had rather more influence on the overall PNMR, the correlation coefficient was negative (−0·51, $P<0{\cdot}10$). This is in line with the findings of studies by obstetricians that the reduction in mortality has not been dependent on a rising caesarean section rate (O'Driscoll & Foley 1983; Francome & Huntingford 1980). Again there is no consensus on a 'correct' rate, for in the English regions it varied in 1982 from 8·4% to 12·2% and is higher in parts of Scotland

Other interventions

Comparable records for other interventions or aspects of obstetric management, such as the use of anaesthetic, analgesic or other drugs, fetal monitoring or ultrasound scanning, are not

Table 9. Rates of interventions associated with spontaneous and induced labours in 1979, 1980 and 1982*

Intervention	Induced (n = 350 030)	Spontaneous (n = 1 375 790)	Total (n = 1 725 820)
Forceps (%)	16·9^{+}	9·6	11·1
Vacuum (%)	1·0^{+}	0·5	0·6
Breech extraction (%)	1·6^{+}	1·1	1·2
Non-elective caesarean section (%)	7·8^{+}	4·0	4·8

$^{+}$Level of significance $P<0{\cdot}0001$.

*Sources: OPCS Monitor (1984*b*; 1984*c*).

available. Their net benefit had not been established before their introduction and their correlation with the PNMR cannot be investigated retrospectively. Yet the implication is that at least some of them have an adverse effect on mortality and account for that part of the strong negative correlation between the PNMR and hospitalization, the proxy for obstetric interventions as a whole, not accounted for by the correlations between the PNMR and induction, forceps delivery and caesarean section.

Effect of interventions on outcome

Results of the 1970 survey show that mortality and morbidity were higher when interventions were used than when they were not. The claim that they were only used to forestall an even worse outcome cannot be sustained, induction, for example, having been widely used in uncomplicated cases. The evidence is that they are more likely to be thought necessary in a hospital setting than when similar conditions arise in the GPU, even attached GPU, or at home.

Indeed the conditions themselves have been found to arise more frequently in hospital. In a Dutch study comparing the outcome where women with the same pre-delivery risk opted freely for delivery at home or in hospital, significantly more complications during delivery occurred in those who opted for hospital delivery. 'The fact that in a hospital . . . the very surroundings and equipment may give rise to iatrogenic complications is apparently overlooked' (Damstra-Wijmenga 1984).

In a comparison between two well matched groups of low-risk women booked for delivery in a consultant unit or the attached GPU of the same Oxford hospital (Klein *et al.* 1983), the actual usage of various obstetric procedures was more frequent in the consultant unit, even in the non-induced sub-groups The interventions inflicted on women in the consultant unit were shown to be unnecessary and on the whole harmful, compared with the simplicity and safety of delivery of similar low-risk women in the attached GPU.

Interventions, such as analgesia, including epidural, anaesthesia and electronic fetal monitoring as well as forceps delivery and caesarean section, are significantly more likely to follow induced than spontaneous labours. This relation was measured in a comparison of 200 deliveries where labour started spontaneously with 200 closely matched deliveries where labour was induced, both groups being free of medical and obstetric complications. Only 68% of the induced compared with 99% of the spontaneous group went on to have a spontaneous delivery (Yudkin *et al.* 1979).

All the interventions have, to a greater or lesser degree, adverse consequences for the baby, increasing the risk of fetal distress and neonatal difficulties in breathing and sucking (Chamberlain *et al.* 1975). The 1970 survey found that breathing difficulties were much more often suffered by, and proved fatal to, babies born in hospital, despite the fact that a much greater proportion of them were transferred to special care units (Tew 1980) In the Dutch study (Damstra-Wijmenga 1984) infants born in hospital were three times more likely to need special care. In the Oxford study (Klein *et al.* 1983) babies of normal weight born in the consultant unit were much more likely to have low Apgar scores, to need intubation and care in a special unit.

Effect of interventions on gestation and birthweight

By definition, induction and elective caesarean section shorten gestation and produce lighter babies, factors associated with higher mortality. Routine statistics do not permit their effect to be measured, but in the 1970 survey the proportion of induced births was not much less for births up to than over 38 weeks of gestation, 22% against 28%. In both gestation groups the PNMR was much higher following induction, 91·7 against 64·3 up to 38 weeks, 11·8 against 6·7 over 38 weeks. More of the births in hospital (12·1%) than in GPU/home (6·4%) took place before the 38th week of gestation. While some of this excess may have been due to hospitals admitting as transfers from GPU/home an excess of threatened premature deliveries which they did not manage to postpone, the remaining excess was probably the result of induction. The explicit data of the 1958 survey show that gestations under 38 weeks were very significantly more frequent among births booked for hospital than for GPU/home, including transfers, and the specific PNMR for booked births were higher for the hospital group at all gestations under 40 and over 41 weeks. The corresponding specific PNMR cannot be estimated for 1970 because the necessary data were not published, nor can the overall

PNMR be standardized to measure how much of the excess PNMR in hospital was due to their greater proportion of births of short gestation. Nationally the induction rate was lower in 1982 than in 1970, but it is not known how much this has affected the excess in hospital of births of short gestation.

The effect of induction on birthweight was not reported in the 1970 survey, but it was probably the main reason why hospital births included 38·6% weighing <3000 g and 10·1% weighing <2500 g, compared with 19·4% and 3·2% respectively in GPU/home. In hospital, where induction was more frequently used, the percentage of lower-weight births had increased since 1958 when it was 28·1 for actual deliveries (or 26·3 excluding transfers) for births up to 3000 g and 8·8 (or 7·1 respectively) for births up to 2500 g. In contrast the percentages in GPU/home, where induction was little used, decreased after 1958 when they were 21·1 for actual (or 23·1 for booked) births up to 3000 g and 4·5 for actual (or 6·0 for booked) births up to 2500 g.

These results suggest that the factors which led to the decrease in the PNMR led also, in the absence of intervention, to a decreased proportion at low weight, but that this consequence was more than offset by the increasingly frequent use of induction. They point to one of the mechanisms through which the decline in the national PNMR was kept smaller than it would otherwise have been. The hypothesis that factors which should have reduced the proportion of low-birthweight babies over time were offset by the increased smoking of pregnant women requires the unlikely assumption that smoking trends moved strongly in opposite directions according to place of delivery.

In the 1970 survey the specific PNMR at each birthweight were not published for each place but, assuming that they were everywhere in the same ratio to each other (following the model illustrated in Table 6), they must have been more than twice as high in hospital for every birthweight group including the lightest. Standardizing (as in Appendix 2) to allow for the greater proportion of low-birthweight babies in hospital would reduce the crude PNMR in hospital from 27·8 to 22·9 and raise the crude PNMR in GPU/home from 4·9 to 9·6, still leaving a formidable disparity (Table 3). The specific PNMR at all weights up to 3000 g were higher for hospital in 1958 also, whether by place of delivery or by place of booking.

By 1983 the specific PNMR for babies <1500 g had fallen to less than half what it had been in 1958 (834 to 384) and obstetricians and neonatologists would like to claim the credit for this remarkable improvement. But by 1983 the PNMR for births weighing 1500–2499 g had fallen to one-quarter of the 1958 level and for weights of ≥2500 g to one-fifth. While the PNMR has been reduced by certain elements of obstetric care, for example, in treating and preventing Rhesus iso-immunization, and in preventing rubella and the birth of some babies with mortal malformations, the evidence is that the reduction in PNMR overall and therefore at most weights has not been brought about by obstetric management as a whole. It must, therefore, be questioned how much the relatively smaller reduction in the PNMR for the tiniest babies is due to obstetric or paediatric care and how much to the non-obstetric factors to which the improved survival of the other babies is due. Might it be that even the tiny babies would now survive better without the aid of high technology, as Dr Edgar Rey has found in Bogota (Gillie 1984)?

High technology may, however, have been the reason why in New Zealand in 1978–1981 the PNMR for the small group of babies weighing <1500 g was slightly, though not significantly, lower in the units providing the most highly specialized obstetric and neonatal care. In contrast, for babies weighing ≥1500 g, the PNMR was significantly lower in maternity units staffed by midwives and general practitioners than in the specialist hospitals, thus confirming that in the great majority of cases birth is safest where interventions, even modern and sophisticated ones, are least (Rosenblatt *et al.* 1985).

Experience in Finland, 1977–1981, was similar. The specific PNMR of babies weighing >2500 g was significantly highest ($P<0{\cdot}001$) in the most specialized hospitals. The PNMR was significantly lower ($P<0{\cdot}01$) for these hospitals only at birthweights 1001–2000 g (Hemminki 1985). It is not stated whether this advantage was offset to any extent by an excess of neonatal or post neonatal deaths of basically sick babies. The most specialized hospitals had the highest proportion of low-birthweight babies, but some of this excess may have been of basically healthy babies induced before term and these may have contributed to the relatively low PNMR.

What has made birth safer?

The results from all sources, routine official statistics, national surveys and specific studies, consistently point to the same conclusion, namely that obstetric intranatal interventions have made birth less safe, not more safe, for the vast majority of cases. No other hypothesis has been proposed that fits the facts so completely. Nor is this a recent phenomenon: it continues the experience of earlier centuries (Tew 1986). Since this is so, some other powerful coincidental factor must explain the remarkable contemporaneous decline in the national PNMR. This factor is almost certainly the improvement in the health status of parents, especially mothers, and in their environment, for, as in every other living species, healthy offspring are most likely to come from healthy parents.

Health status improves and death rates fall when the standard of living, the quality of diet and shelter, improves. The importance of this factor is witnessed by differences in death rates between countries, between social classes and between periods. In England and Wales the effects of improvements in the standard of living in the nineteenth century were seen in the sudden and sustained decline in the death rate after 1870. This decline was experienced by all age-groups except infants whose mortality rate did not start to fall till after 1900 and then most of the decline was in post-neonatal mortality. It was not really until the 1940s that there was a substantial proportional fall in the PNMR and this accelerated rate of decline did not happen again till after 1975. Clearly the PNMR responds most noticeably to improvements in the standard of living only after a time-lag. Mothers in the 1970s, as infants in the 1940s and 1950s, had benefited from the improved standards, especially diet, just as their mothers, grandmothers and indeed great-grandmothers had, as infants, benefited from improved standards since before 1900. The higher level of unemployment in the 1980s shows no sign of offsetting the improved health status of mothers built up over several generations.

This inference about PNMR from the English official statistics is confirmed by findings in Aberdeen, where infants of low birthweight tended to have mothers and grandmothers who also had been of low birthweight. 'Reproductive efficiency is related to the mother's health and physique, which in turn is related to the quality of the environment in which she grew up . . There is of course, a limit to what can be achieved in one generation in improving the level of health and physique' (Baird 1985). There is evidence too of generation improvements in the incidence of congenital malformations, in particular anencephaly, in Britain (Baird 1985; Owens *et al.* 1981) and also in Holland (Kloosterman 1978).

If then the improved health status of mothers has led to a reduced incidence of perinatal death and anencephaly, it ought to have led to a reduced incidence of low birthweight. 'Initially in the more affluent societies the rate of low birthweight fell and this contributed substantially to a fall in numbers of stillbirths and early infant deaths. Since the 1950s, however, the rate of low birthweight has remained fairly constant in Britain and in many other developed countries' (Illsley & Mitchell 1984). The explanation of why the percentage of low-weight births did not diminish most probably lies in the counteracting effect of induction and elective caesarean section.

It has turned out to be extremely unfortunate for medical understanding that the improvement in PNMR, which was bound to follow the improvement in health status, should have coincided with the expansion of obstetric intranatal management, for it was then all too easy to attribute the former change to the beneficial consequences of the latter. The coincidence happened in many countries, so that the mistaken attribution of cause and effect has been worldwide. The majority of obstetricians, everywhere, have become convinced that the natural process of birth is fraught with dangers which their increasingly sophisticated technological interventions are increasingly capable of minimizing. Amazingly, they have managed, without producing any valid supporting evidence, to persuade the majority of people, medical and lay, that they are right and the maternity service has been organized in accordance with this unjustifiable hypothesis.

There are now relatively few obstetricians and general practitioners who subscribe to the principle that for healthy women giving birth is a normal physiological process, which obstetric intervention cannot improve though it can harm, and that only in a very small proportion of deliveries do complications arise which obstetric interventions can positively help. '. . . the ideal obstetrical organization brings aid to women and children who need help (the pathological group) and protects the healthy ones against unnecessary interference and human meddlesomeness' (Kloosterman 1978). The key question today for an obstetrician or midwife is 'how not to disturb the physiology of the birth process' (Odent 1984). This is the principle which all the evidence supports but which most obstetricians recoil from accepting as right.

On the basis of experience to date, providing more obstetric facilities will not further reduce perinatal mortality. There would be more hope of achieving this if resources could be devoted instead to improving the standard of living of the least healthy parents and children in the population, towards 'the elimination of this continuity of social disadvantage' (Baird 1985). This was recommended in the Black Report (Black *et al.* 1980). It has largely been achieved in Sweden with the desired effect on perinatal mortality.

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Appendix 1

To show how the overall still-birth rate (SBR) increases when the proportion of births at higher risk increases, and conversely, how the overall SBR decreases when the proportion of births at lower risk increases, without in either case any change in the specific rates in the sub-groups—the real risk The example corresponds closely to reality, for it uses the actual SBR and the appropriate total numbers of births at home in 1970 and 1978, when the number in the 'problem' sub-group must have been at least 2000, most of them to teenage and unmarried women or other first births.

Year	No. of births	Proportion	Specific SBR per 1000 births	Product
1970				
Lower risk	101 000	0·98	4·0	3·9
Higher risk	2000 (est)	0·02	34·0	0·7
All	103 000	1·00	4·6 (actual)	4·6
1978				
Lower risk	8000	0·80	4·0	3·2
Higher risk	2000 (est)	0·20	34·0	6·8
All	10 000	1·00	10·0 (actual)	10·0

Taken from Tew (1981), Health and Social Service's Journal, 17 April, 446.

Appendix 2 appears on next page

Appendix 2

To show how perinatal mortality rates (PNMR) are standardized to allow for different proportions of births in each place, when the specific PNMR in each place are not known—the indirect method of standardization. The age specific PNMR for the survey population and the number of births in each age-group at each place are known. The direct method of standardization is illustrated in Table 1B

Age-group (years) A	Survey PNMR B	Hospital Births C	Hospital Expected deaths $\frac{B \times C}{1000}$	GPU/home Births D	GPU/home Expected deaths $\frac{B \times D}{1000}$
<20	28·6	1231	35·2	341	9·8
20–24	18·0	3830	68 9	1777	32 0
25–29	19·3	3214	62·0	1606	31·0
30–34	20·9	1685	35·2	685	14·3
>34	35 7	1126	40·2	223	8·0
All ages	21 4		241·5		95·1
Actual deaths			310		23
Standardized PNMR					
Survey PNMR × $\frac{\text{Actual deaths}}{\text{Expected deaths}}$			$21{\cdot}4 \times \frac{310}{241{\cdot}5} = 27{\cdot}5$		$21\ 4 \times \frac{23}{95\ 1} = 5{\cdot}2$

Data from Chamberlain *et al* (1978) Table 5·8

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Place of delivery: a review

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Summary. Policies about place of delivery have tended to be formulated without either looking at existing evidence or doing new research into the relative safety for women and babies of delivery in different settings. This article reviews published research on the subject, and finds that many of the data required have not been collected. Furthermore, many analyses fail to take account of selection biases or differences in the birthweight distribution and the incidence of congenital malformations among babies born in different settings. Nevertheless, some tentative conclusions can be drawn. The available evidence does not support claims that, for the baby, the iatrogenic risks of obstetric intervention outweigh the possible benefits. At the same time, there is no evidence to support the claim that the shift to hospital delivery is responsible for the decline in perinatal mortality in England and Wales nor the claim that the safest policy is for all women to be delivered in hospital.

Informed debate on the relative merits of different places of birth has always been hampered by a lack of reliable statistical and epidemiological information. As Florence Nightingale commented in her 'Notes on Lying-In Institutions' (Nightingale 1871):

> *'It must be admitted, at the very outset of this enquiry that midwifery statistics are in unsatisfactory condition . . . But, with all their defects, midwifery statistics point to one truth, namely that there is a large amount of preventable mortality in midwifery practice, and that, as a general rule, the mortality is far, far greater in lying-in hospitals than among women lying-in at home.'*

When, in 1927, live births registered in England and Wales were tabulated by place of delivery for the first time, 85% of births took place at home with the remaining 15% occurring in hospitals, nursing homes, maternity homes and Poor Law institutions (General Register Office 1929). By 1970, the position was reversed. The move from home to institutional delivery has been accompanied by changes in the institutions themselves and with the type of care provided. The trend has been towards consultant obstetric care in large specialized units. In 1984, nearly all deliveries (94·9%) took place in NHS hospitals with consultant obstetric facilities, 1·0% occurred at home and 2·9% took place in NHS isolated general practitioner (GP) units (Office of Population Censuses and Surveys 1985)

Successive committees have advocated increasing the proportion of hospital deliveries on the grounds that this offered the greatest safety for all mothers and babies but none reviewed the evidence in any depth (Macfarlane 1985). Analyses quantifying the associations between places of delivery and the outcome of pregnancy have called this assumption into question. This paper describes and assesses the methodological approaches taken in many of these studies, and details the conclusions that

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seem justified in the light of the problems associated with the methods used. It is based on parts of a fuller and longer review done in conjunction with Dr Tony Ellam, copies of which are available from the National Perinatal Epidemiology Unit.

Perinatal mortality rates as measurements of outcome

When Florence Nightingale noted that mortality was higher in women who were delivered in hospital she was referring to maternal mortality. Today maternal deaths are very rare in developed countries and consequently the most commonly used measure of the outcome of pregnancy is the perinatal mortality rate. Other variables such as morbidity in the mother and in the baby and the views of those receiving care have also been used to a limited extent, but these are more difficult to measure and assess.

Although crude perinatal mortality rates from all causes are frequently employed as indicators of the quality of care for a given place of delivery, their use in this way can be misleading. The two factors most strongly associated with perinatal mortality, in a statistical sense, are the incidence of lethal congenital malformations and the proportion of babies weighing less than 2500 g. In 1984, 18% of the perinatal deaths in England and Wales had congenital malformations as their 'underlying cause'. Furthermore, when deaths attributed to these causes were excluded, 66% of stillbirths and early neonatal deaths were of babies weighing under 2500 g (Office of Population Censuses and Surveys 1986).

The incidences of congenital malformations and low birthweight vary according to a whole range of demographic, socioeconomic and biological factors, which are largely beyond the control of health services. It is therefore inappropriate to use crude perinatal mortality rates as indicators of the quality of maternity care, so in some studies attempts have been made to derive more sensitive measures which take selected factors into account.

As many congenital malformations cannot currently be prevented once conception has occurred, deaths attributed to such abnormalities should be excluded from any analyses investigating the effectiveness of care up to and around the time of delivery. Likewise, when comparing groups of babies, some attempt should be made to allow for differences in the proportion of low birthweights. A number of methods for doing so have been described (Mallet & Knox 1979; Macfarlane *et al.* 1980; Wilcox & Russell 1986). Regrettably, crude perinatal mortality rates have been used in many analyses related to the place of birth, and thus must be considered within the scope of this review.

Studies of trends in perinatal mortality in relation to changes in place of delivery

In the introduction to the second report of the Maternity Services Advisory Committee (1984), the chairman, Alison Munro echoed the views expressed by earlier committees when she wrote:

> *'The practice of delivering nearly all babies in hospital has contributed to the dramatic reduction in stillbirths and neonatal deaths and to the avoidance of many child handicaps.'*

A number of detailed analyses of the temporal association between the falls in both the perinatal mortality rate and the proportion of births at home do not, however, support Alison Munro's claim. Instead, they suggest that the relation is likely to be coincidental rather than causal.

One of these used data from the Cardiff Births Survey (Chalmers *et al.* 1976), and showed that while the proportion of births occurring at home fell from 1 in 5 in 1965 to 1 in 100 in 1973, there was no statistically significant decrease in the crude perinatal mortality rate, nor in death rates attributed to causes which were deemed preventable. Another study used maternity records of women booked for delivery in hospitals with consultant obstetric facilities in Newcastle upon Tyne during the period 1960–1969 This analysis revealed that the perinatal mortality rate declined uniformly among both home and institutional births (Barron *et al.* 1977).

A study of the association between the combined stillbirth and neonatal mortality rates and hospital delivery rates between 1956 and 1969 in local authority areas of England and Wales (Fryer & Ashford 1972) showed that in each year from 1956 to 1967, areas with above average hospital delivery rates tended to have below average mortality rates. The strength of this association weakened over time, however, and the position was reversed in 1968 and 1969. As the proportion of hospital deliveries increased even further between 1970 and 1973, the association with low mortality rates became even more tenuous (Ashford 1978). Analyses subdivided by birthweight showed that throughout the entire period, higher hospital delivery rates tended to be associated with lower mortality rates in the group weighing less than 2501 g. On the other hand, in babies weighing over 2500 g, high mortality rates tended to be associated with high hospital delivery rates from 1964 onwards (Fryer & Ashford 1972; Ashford 1978).

Looking in more detail at the associations between the trend towards hospital delivery and declining perinatal mortality, between 1969 and 1981, Marjorie Tew carried out a regression analysis which showed that in the years when hospitalization rates increased most, perinatal mortality fell least (Tew 1986). On the basis of this strong negative correlation, Tew (1986) concluded that the overall perinatal mortality rate would have shown a greater fall if hospital delivery rates had increased less. A strong statistical association is not necessarily indicative of a causal relationship. In the absence of supporting evidence therefore, it would seem just as inappropriate to conclude that increasing hospital delivery rates retarded the fall in the overall perinatal mortality rate, as it would be to conclude that they caused the fall.

Until 1975, perinatal mortality rates for England and Wales subdivided by place of delivery were available only from the cross sectional birth surveys done in 1958 and 1970. Despite variations in scale and location these surveys both revealed a substantially lower perinatal mortality rate for domiciliary deliveries (Butler & Bonham 1963; Richards *et al.* 1970; Chamberlain *et al.* 1975) In the most recent, the 1970 British Births Survey, the perinatal mortality rate for singleton deliveries occurring in consultant obstetric units was 27·8 per 1000 births compared with 4·3 for births taking place at home and 5·4 for births in isolated GP units. Clearly, the findings of such surveys do not represent unbiased estimates of the risk of perinatal death attributable to the place of delivery, as no account has been taken of the complex biological, social and medical selection process which influenced the choice of place of birth.

Factors influencing selection can confound analyses by being related to both the place of delivery and the outcome. Thus, it is misguided to consider the effect of the place of birth on the outcome of pregnancy in isolation from the factors which lead different women to give birth in different locations, a point which was forcefully expressed by the British Medical Association (1936):

> . . . *maternity and its conduct are not concerned merely with attendance during the actual process of delivery, but comprise supervision from first to last—from the time that changes consequent upon conception manifest themselves until the return to normal some short time after childbirth. It is obvious that this whole period and event cannot be isolated from the rest of the health history of the mother, whether before, during or after the period of actual pregnancy and parturition'.*

The technique used most often in attempts to control for selection biases has been to standardize measures of outcome for the different places of delivery to try to take account of variations in the proportion of women (Tew 1985) or infants (Ashford 1978; S. J. Senn, unpublished observations) possessing certain characteristics associated with an increased risk of perinatal problems.

A number of standardizations of this type, using data from both the 1958 and 1970 Births Surveys, are described in this issue by Tew (1986) who is a strong advocate of this approach. Most of these analyses have involved standardization for single risk factors, but in more recent work two risk scores, which are essentially weighted sums of a variety of risk factors, have been used. These antenatal and labour prediction scores (APS and LPS respectively) were based on 'data related to the biological and social factors constituting risk' identified in the 1958 survey and applied to data from the 1970 survey (Chamberlain *et al.* 1978).

Although a greater proportion of hospital births had high scores in the 1970 survey, when perinatal mortality rates for hospital and domiciliary deliveries were standardized to adjust for the proportions of births in different risk categories, defined by the antenatal and labour prediction scores, Tew (1986) found that her standardization only explained a small part of the excess mortality observed for hospital births.

Although raised perinatal mortality rates in the 1970 survey were associated with higher antenatal and labour prediction scores, these scoring systems have never been widely validated using data from other data sets (Newcombe & Chalmers 1981). Hence, it is possible that it is their poor predictive ability which accounts for some of the unexplained differences between standardized rates, as noted by Tew (1986).

It has been suggested that analyses based on this type of approach can be misleading because of the subtle selection biases for which it may not be possible to control, 'even when considerable quantities of descriptive data are available for statistical adjustment' (Murphy *et al.* 1984). Furthermore, epidemiological studies, both in the perinatal (Elwood 1976; Rose & Marmot 1981) and cardiovascular fields, which have attempted to explain mortality differentials in terms of known risk factors have often failed to account for even half of the observed differences in mortality. Caution is therefore required in the interpretation of the findings of this type of analysis and Tew (1986) may have been over hasty in concluding that the unexplained difference between perinatal mortality rates for hospital and domiciliary deliveries is simply the result of iatrogenic mortality arising out of the way obstetrics is practised in hospitals.

In addition to the difficulties posed by selection biases in choosing an appropriate place of delivery, analyses based on the actual place of delivery also fail to recognize that some women may not give birth in the place they had intended. For example, a woman booked for delivery at home may, after an antepartum haemorrhage, be diagnosed as having placental abruption and be transferred for delivery in a consultant unit. Alternatively, a primigravid woman booked for delivery in hospital may fail to recognize her preterm labour and given birth at home unaided after a pregnancy of 28 weeks.

A survey to determine the intended place of delivery of all births occurring at home in 1979 (Campbell *et al.* 1984) found that, of these births, only two thirds had been booked for delivery at home. The perinatal mortality rate for planned home deliveries was 4·1 per 1000 while for births at home which were planned to occur in consultant units it was 67·5 (Table 1). In all groups, mortality was lower in babies born to parous women, and it was particularly low for parous women having planned home deliveries.

Since 1977, the overall perinatal mortality rate for births at home has been higher than that for consultant units. It was suggested (Tew 1981) that this effect might be an artefact: with the decline in overall numbers of home births, an increasing proportion would be unplanned births at home (Campbell *et al* 1982). The results of the Home Births Survey, together with the findings of other work (Murphy *et al.* 1984), tend to support this hypothesis.

There is no general agreement about whether the intended place of delivery should be defined as that originally booked for delivery or that intended immediately before the onset of labour. If antenatal care differs significantly between groups categorized according to the intended place of delivery, in ways which are likely to influence perinatal outcome, it has been suggested that comparisons should be based on groups defined according to the place where the woman was booked for delivery (Murphy *et al.* 1984).

Classifying births according to the place booked for delivery rather than the actual place of birth, as findings of four surveys summarized

Table 1. Number (%) of births and perinatal deaths by intended place of delivery for all births occurring at home, England and Wales, 1979

Intended place of delivery	Births		Stillbirths and early neonatal deaths		Perinatal deaths per 1000 total births	
	n	(%)	*n*	(%)	Rate	95% confidence interval
Home	5917	(67)	24	(11)	4·1	(2·4–5·7)
Consultant unit	1303	(15)	88	(41)	67·5	(53·9–81·2)
General practitioner bed	546	(6)	7	(3)	12·8	(3·4–22·2)
Unbooked	295	(3)	58	(27)	196·6	(151·3–242·2)
Not known	795	(9)	36	(17)	45·2	(30·8–59·7)
Total	8856	(100)	213	(100)	24·1	

Table 2. Perinatal mortality by place of delivery and place of booking. the results from four studies

Reference	Location and period of study	Crude perinatal mortality rates					
		Place of delivery			Place of booking		
		Hospital	GPMU	Home	Hospital	GPMU	Home
Fedrick & Butler (1978)	Britain, 1958*	11·46	10·70	6·80	8·70	12·00	9·25
Cookson (1963)	Gloucestershire, 1953–1962	46·92		7·59	28·57		24 12
Hobbs & Acheson (1966)	Oxford, 1962–1964	26·00†	11·0		19·00	20 00	
Woods (1981)	Gwynedd, 1946–1970	52·00	8·40	18·90	36·70	23·70	19·70

*See text for exclusions from the numerator and denominator of these rates

†Includes a small proportion of deliveries for which there was no intended place of delivery

GPMU, General practitioner maternity units.

in Table 2 illustrate, tends to decrease the risk of perinatal death associated with hospital delivery and increase the risk for births booked for delivery at home or in GP maternity units. These findings are inconclusive in that, with the exception of the study by Woods (1981) for which raw numbers were not published, there is no statistically significant difference between the mortality rates for hospital booked births and those booked for delivery at home and/or GP maternity units.

The study by Fedrick & Butler (1978) differs from the rest in that their analysis of data from the 1958 Perinatal Mortality Survey was confined to three relatively homogenous groups of women with a low predicted risk of perinatal death: primiparae who remained normotensive throughout; primiparae who were not normotensive throughout and women of parity 1, 2, and 3 who were normotensive throughout. In this way, bias resulting from the selection of women at high risk for hospital delivery should have been reduced. Although the authors reported that 'booking for NHS hospital delivery was associated with a consistently lower death rate ($P<0{\cdot}001$) than booking for domiciliary or some other type of confinement,' this level of statistical significance was only achieved by combining death rates for all deliveries outside NHS hospitals within the three groups, and comparing these with the rates for NHS hospital deliveries. When the results for the three groups are pooled according to the booking for delivery (as in Table 2) there is no statistically significant difference between death rates for births booked for home or hospital delivery (Tew 1978).

Tew (1978) has long maintained that it is only valid to compare perinatal mortality rates by *actual* place of delivery because women booked for delivery at home, but who gave birth in hospital, are exposed to interventionist techniques employed in consultant obstetric units, which, she asserts, increase the risk of perinatal death.

There is a considerable body of evidence which shows that transfer to hospital, particularly in labour, is associated with a high death rate (Butler & Bonham 1963; Hudson 1968; Woodall 1968; Rutter 1964; Rees 1961). Transfer to hospital usually arises because of the emergence of some problem such as, for example, placental abruption during late pregnancy or labour. This is likely to have an adverse effect on the outcome of pregnancy, and requires obstetric intervention. Thus, it is to be expected that babies born to women in this group would experience a higher mortality than those born to women delivered at home as planned. Tew (1986) has suggested that the perinatal mortality for women transferred should not exceed that for those remaining at home by more than a factor of three. This was based on the overall perinatal mortality rates for all babies in the 1970 survey whose deaths were attributed to complications which would be likely to have led to transfer to hospital had the woman been booked for home delivery. In fact, the perinatal mortality rate for babies born to women transferred was six times greater than for those remaining at home in the 1958 survey and 12 times greater in the 1970 survey.

Tew (1986) has inferred that the very elevated mortality rates in the transferred group are simply a consequence of increased obstetric intervention. Her calculations not only exclude relevant data before labour but also are based on speculations as to the reasons for transfer and more fundamentally on the assumption that the mortality associated with complications arising in women who intend to give birth at home, but were transferred, would be the same as that for women who intended to give birth in hospital. On the face of it this might appear reasonable, but it ignores the possibility that any delay in obstetric intervention is likely to be greater in those being transferred from home and that this delay may well lead to a greater risk of death. Furthermore, the increase observed between the two surveys in the mortality for transfers could simply have been because deaths which would have occurred at home in 1958 were occurring in hospital by 1970.

This contention by Tew (1986) is not supported by the findings of a survey comparing outcomes of low risk women booked for delivery in two different systems of maternity care: shared care (consultant unit) and community midwife and GP care (integrated GP unit). That study found that the women transferred from the GP unit to the consultant unit as the result of some emergency arising during labour had outcomes which were as good as, or better than, those women who had the same initial low level of risk but were booked for delivery in the consultant unit (Klein *et al.* 1980).

With the reduction in perinatal mortality, epidemiological interest has become increasingly focused on perinatal morbidity and how this might be a possible indicator of the quality of obstetric care. Studies of perinatal morbidity in relation to the place of birth are few but nevertheless merit consideration within the context of this review. The studies we have mentioned so far have been done within the United Kingdom, but because of the dearth of information about morbidity, we have also considered studies from other countries under this heading.

The 1970 British Births Survey compared babies born in different settings and defined as unfit. Babies born at home suffered more from jaundice and minor infections than those born in NHS hospital and GP maternity units. Conversely, babies born in these institutions had a larger percentage of more serious conditions such as congenital malformations, fits, cerebral signs and respiratory difficulties (Chamberlain *et al.* 1975).

Similarly, a study of cerebral palsy among children born in the Northern Region of England between 1960 and 1975 showed lower rates of cerebral palsy among children born at home or in small units without resident staff than in children born in consultant units, even when differences in the birthweight distribution were accounted for (Jarvis *et al.* 1985).

A study of 1692 women at low risk who had babies in Groningen Municipality in the Netherlands in 1981 showed the women who opted to give birth at home experienced fewer complications during pregnancy, labour and the puerperium than those who chose to give birth in hospital, even when parity was taken into account. Women in the study population initially had a free choice as to where they gave birth, either in hospital (a 1-day stay or a 7-day stay) or at home. Then if any abnormality arose during pregnancy in those booked for delivery at home, their booking was changed to hospital. In babies born without complications, morbidity leading to referral to a special care unit was lowest in those born at home and highest in those born in hospital (Damstra-Wijmenga 1984).

The findings of these descriptive studies are of interest, but because no attempt has been made to control for selection biases, it is not possible to assess the extent to which differences in morbidity can be attributed to differences in the place of birth.

Two other studies have attempted to contrast morbidity in similar populations of women at low risk giving birth in different settings. A study in Oxford in 1978 compared the outcomes for low risk women booked for delivery either within a system of consultant-based shared care or with community midwife and GP-based care (Klein *et al.* 1980). It was found that in infants born to nulliparous women, the proportion with low Apgar scores and requiring intubation was lower in those booked for delivery in the GP unit. The use of epidurals and pethidine was considerably higher in nulliparous women booked for delivery in the consultant unit under the shared care system. Although the authors conclude that it is not possible to say which procedures used in the consultant unit might have accounted for observed differences in neonatal outcomes, they do suggest that the 'use of analgesia and perhaps anaesthesia merits further attention' (Klein *et al.* 1983). A follow-up study done in 1981 found fewer differences between patterns of care in labour in the two systems, but did not cover large enough samples of women to make a comparison of the outcomes in the two groups (Klein *et al.* 1985).

A study in the United States matched 1046 women, who immediately before the onset of labour intended to give birth at home, with a similar group of women intending to give birth in hospital (Mehl 1978). The women were matched for age, education, socio-economic status and obstetric risk factors. Although the incidence of episiotomy was nine times higher among hospital deliveries, there was a statistically significant excess in the number of 'second, third, and fourth degree lacerations' in women delivered in hospital compared with those who gave birth at home. A significantly greater proportion of babies born in hospital had birth injuries, neonatal infections, respiratory distress lasting ≥12 h and non-congenital neonatal complications. There were, however, no significant differences in mortality or neurological impairment.

For every delivery, the desired outcome is a healthy mother and baby. If by health we mean 'a state of complete mental, physical and social well-being and not merely the absence of disease' (World Health Organization 1948) then we must also take into account the degree to which parents, and in particular, mothers, feel satisfied with the delivery. The rapid and sustained decline in the proportion of births at home might be taken as an indication that women prefer to give birth in hospital. The available research findings suggest, however, that the opposite may be true.

Unfortunately, most of the surveys conducted to determine women's preferences with respect to the place of birth have involved small, non-random groups of women. In all of the surveys where women have experienced both home and hospital delivery, however, the vast majority preferred home (Gordon & Ellias Jones 1960; Alment *et al.* 1967; Fleury 1967; Goldthorpe & Richman 1974).

A postal survey based on a random sample of 2400 births in England and Wales in 1975 found that 92% of women who were delivered at home but had had their previous baby in hospital preferred the home delivery. Only 23% of those who had their baby in hospital but the previous baby at home preferred hospital (O'Brien 1978).

More recently, a postal questionnaire was sent to all 192 women living in Nottingham Health District who gave birth successfully at home in 1980 and 1981, and to a random sample of 365 women who had a successful hospital delivery during the same period (Caplan & Madeley 1985). Overall, 90% of those who were delivered at home and 88% of those who gave birth in hospital said that they would like to have their next birth in the same place again, but many women in both groups did not answer this question 'for reasons which remain obscure'.

These studies are also almost certainly subject to the selection biases which beset place-of-delivery analyses. Women who have had a previous delivery in hospital which they found unsatisfactory are more likely to opt for a home birth for subsequent deliveries than those women who were satisfied with their hospital deliveries. The same would apply to women having negative experiences when giving birth at home. Given the huge disparity in the absolute numbers of women giving birth at home and in hospital, however, the flow of disenchanted mothers is largely going to be from hospital to home. Thus, the population of women who gave birth at home may contain a disproportionate number of women who were dissatisifed with hospital delivery.

All of the work reviewed in this paper has been based on observational data. Even in those studies where attempts have been made to control for the selection biases which confound place of delivery analyses, it is still difficult to assess the extent to which differences observed in outcomes are directly attributable to differences between places of birth. The only unbiased means of assessing the mortality and morbidity risks associated with different places of birth would be to conduct a randomized controlled trial. Quite apart from the practical difficulties in mounting such a trial, the numbers required to participate in order to show a significant difference in perinatal mortality between the two groups are now prohibitive (Chalmers 1978; Alberman 1984). It would have been possible to mount such a trial in the 1960s or early 1970s when substantially more women were giving birth at home and it is unfortunate that such an opportunity was missed by the successive committees who made recommendations about the place of delivery.

Conclusions

Our review of place of delivery analyses suggests the following conclusions:

(1) The statistical association between the increase in the proportion of hospital deliveries and the decline in the crude perinatal mortality

rate seems unlikely to be entirely or even mainly explained by a cause and effect relation.

(2) Attempts to explain the higher crude perinatal mortality rates observed for births occurring in hospitals with consultant obstetric facilities before the mid 1970s, in terms of known risk factors, fave failed. In particular, it is not possible to conclude with any degree of confidence that these differences are because women giving birth in hospitals with consultant facilities were, and are, exposed to a greater risk of perinatal death than those giving birth elsewhere This is a consequence of the methodological shortcomings of the use of crude statistics and also because not all risk factors will have been measured and included in the analysis.

(3) The rise in the crude perinatal mortality rate for births occurring at home can almost certainly be explained by the increase in the proportion of unplanned births at home relative to those planned to occur there, as the overall numbers of home births declined.

(4) The Home Births Survey showed that perinatal mortality rates for the select group of women who had planned deliveries at home were very low, particularly for parous women.

(5) There is no evidence to support the claim that the safest policy is for all women to give birth in hospital.

(6) There is some evidence, although not conclusive, that morbidity is higher amongst mothers and babies delivered and cared for in institutional facilities in general and consultant obstetric units in particular. It is possible that for some women the iatrogenic risk associated with institutional delivery is greater than any benefit conferred but this has yet to be proven.

(7) A majority of women who have experienced both home and hospital deliveries prefer to have their babies at home, although this group may contain a disproportionate number of women who have sought home delivery after a hospital delivery with which they were dissatisfied.

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A comparison between the organization of obstetrics in Denmark and The Netherlands

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Summary. A comparison was made between two types of obstetric organization: total hospitalization as in Denmark, and a system that allows a choice between hospital and home delivery, provided there are no medical contra-indications, as in The Netherlands. Until the end of the 1950s, the current Dutch view prevailed in Denmark; Denmark changed its organization in the late 1960s and followed the international preference for total hospitalization. This change was not caused by disappointing obstetric results, nor was it the result of strong pressure from pregnant women. The change was associated with a considerable increase in instrumental deliveries. In both countries the perinatal mortality rate decreased continuously but in Denmark the improvement in early neonatal mortality was slightly faster. This difference may have occurred because of insufficient referral in The Netherlands of high-risk pregnancies and deliveries to the fully equipped obstetric departments. The Dutch acceptance of a high proportion of home-confinements is unlikely to be the explanation.

Kloosterman (1978) drew attention to the fact that Dutch obstetric organization does not follow the international view that all births should take place in hospital. The Dutch system is still based on the idea that women with low-risk pregnancies must have a free choice where to give birth to their children (Kloosterman 1983; Huygen 1976). In 1980, 35% of all Dutch babies were born at home.

Kloosterman (1978) postulated that:

(1) the international preference for total hospitalization as the best and safest procedure for mother and child is based on preconceived opinion, not on proven facts,
(2) total hospitalization inevitably gives rise to an increasing number of instrumental deliveries (especially caesarean delivery) and deliveries using sophisticated methods of anaesthesia, and
(3) that the Dutch type of organization is worth continuing, since it enhances both self-confidence in the mother, with more spontaneous deliveries as a result, and maternal attachment.

In contrast to The Netherlands, Denmark recently changed its attitude in accordance with the international view, and went over to total hospitalization and to concentration of obstetrics in large obstetric units. Denmark's recent experience therefore seemed very suitable for comparison with that in The Netherlands. Until the end of the 1950s the organization of obstetric care in Denmark and The Netherlands had many features in common: an acceptance of home-confinements, independent midwives for the care of well selected low-risk pregnancies, and low obstetric intervention rates. Thereafter the strategy in Denmark changed rapidly; total hospitalization was achieved in 1972. In contrast, the policy in The Netherlands stayed the same. In both countries many so-called 'hospital deliveries' took place in small hospitals or 'clinics'.

A commission appointed by the Danish Minis-

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try of Internal Affairs stated in 1956 (Department of Home Affairs 1956) that 'the ideal situation is that pregnant women have a free choice between delivery at home or at a well-equipped institution'. But another commission on the organization of obstetrics in Denmark stated in 1972 (Department of Home Affairs 1972) that even low-risk women should preferably be delivered in an institution (hospital or 'clinic').

A 'clinic' is, in effect, a maternity home which offers no possibility of specialist obstetric care.

The present study was undertaken to elucidate the motivation for changing the Danish organization of obstetrics and whether this change has been associated with more active obstetric intervention, as predicted by Kloosterman (1978), and also whether the organization of the maternity services in Denmark has resulted in better perinatal results than those in The Netherlands.

Methods

Statistics were obtained from the Danish National Board of Health (Sundhedsstyrelsen) Department of Statistics. Comparable figures for The Netherlands were obtained from the Dutch Central Bureau of Statistics (CBS). This information was supplemented by interviews with many Danish and Dutch authorities in the field of obstetrics and by visits to Danish and Dutch university hospitals (Herlev University Hospital, Copenhagen and the Wilhelmina Gasthuis, Amsterdam).

Results

During the period 1960–1980 the percentage of births in institutions increased in Denmark from approximately 50% to 99% and during the same period the corresponding percentage in The Netherlands rose from about 28% to 67% (Fig. 1).

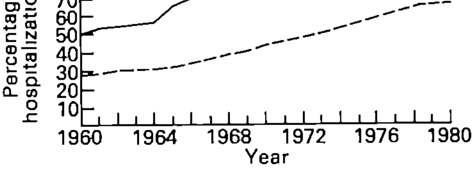

Fig. 1. The increase in hospitalization of deliveries in (———) Denmark and (- - - -) The Netherlands.

Motivation for hospitalization of the majority of births in Denmark

Ingerslev (1962) discussed the motivation for hospitalization of low-risk deliveries. He admitted that complications occur occasionally, but he felt that the life of the mother could be protected by immediate transfer to hospital. Further, he argued that at home a pregnant woman had a midwife at her side all through labour, a service she would not have in hospital, where the midwife often has to look after more than one woman at the same time.

Because of this more intensive care at home, fetal complications in the home should be detected early, and transfer to the hospital could then reduce the risk to the fetus. In the same article, Ingerslev (1962) drew attention to the fact that the social security system (sygekasserne) at that time supported hospitalization because it was cheaper both for the insurance system and the women themselves. Whether it was also cheaper for the community as a whole was not discussed.

During the 1960s the concept of systematic identification of risk factors during pregnancy was very thoroughly discussed. It was thought that by using such a system most of the complications of pregnancy and delivery could be foreseen.

Kaern (1965) obtained excellent results by selecting low-risk cases for delivery in a 'clinic' while the cases at risk were delivered at the St Joseph Hospital in Copenhagen, a well-equipped obstetric department of a big hospital. Kaern (1965) also demonstrated, however, that selection using risk factors could not predict all cases in which complications might occur. With an increasing 'perfectionism' in obstetrics, this problem became more important.

Ingerslev (1970) showed that 12% of 1327 low-risk cases, who were admitted to a 'clinic', were transferred to hospital because of complications. None of these were life-threatening and no maternal or perinatal death occurred. A similar study in Copenhagen county (Falck Larsen, personal communication) showed the same results

In spite of these considerations, Ingerslev (1970) proposed a system in which all deliveries should take place in a department of obstetrics and gynaecology, and the women and the infants could be transferred to 'clinics' or other non-specialized departments after delivery. This idea was adopted by the Danish Society for Obstetrics and Gynaecology and in part by the Danish National Board of Health (Sundhedsstyrelsen).

Effect on the incidence of interventions

The incidence of instrumental deliveries has increased in both Denmark and The Netherlands.

Figure 2 shows the increasing percentage of ceasarean sections and the total number of instrumental deliveries (ceasarean section plus vacuum extractions plus forceps deliveries). There was little difference between the two countries in the period during which they had a comparable organization of obstetric care, but thereafter, the caesarean section rate in The Netherlands doubled from 2% to 4%, while Denmark showed an increase from 2% to almost 11%.

The total number of operative interventions in Denmark is now much higher, almost 20%, while in The Netherlands it is still only 12%.

Both in Denmark and The Netherlands the exact incidence of epidural analgesia during delivery is not known. One can safely estimate that the incidence in The Netherlands will not exceed 2·0% of all deliveries. (Since epidural analgesia is performed in hospitals where fewer than 30% of all deliveries take place, and in six of the largest of these hospitals the incidence of epidural analgesia varied between 3 and 11%, we estimate the overall incidence in 1984 to be less than 2%).

The Danish data relate only to singleton births, and in 1982 the incidence of epidural analgesia was 2·2%. (L. B. Knudsen, personal communication, unpublished statistical data from the Danish National Board of Health).

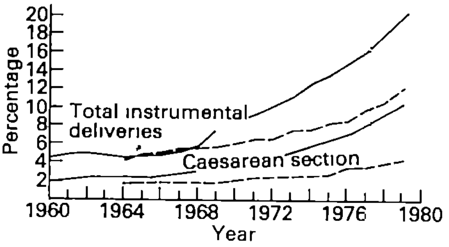

Fig. 2. Instrumental deliveries. See Fig 1.

The improvement in obstetric results

Figure 3 shows that overall perinatal mortality (stillbirths and deaths during the first week of life) has decreased in both countries.

The curves are almost identical until 1965, from there on the Danish results are slightly better, particularly after 1976.

The two components of perinatal mortality are separated in Fig. 4. The still-birth rate has declined at a similar speed in the two countries, although the rate in The Netherlands has been consistently higher than that in Denmark. In contrast, although Denmark had a higher early neonatal mortality rate at the beginning of the time period studied, this fell more rapidly than that in The Netherlands so that, by the late 1970s, the rates were comparable in the two countries.

Birthweight-specific mortality rates are not available for The Netherlands.

Discussion

The percentage of hospital deliveries has increased in both Denmark and The Netherlands although a plateau appears to have been reached in both countries in the late 1970s.

The Danish motivation for hospitalization is the supposition that selection according to risk factors does not predict all complications. This philosophy is underlined once again by two recent Danish studies (Brogaard Hansen *et al.* 1984; Hansen & Christoffersen 1986).

Dutch studies support this view in so far as they also show that 'labour is only normal in retrospect' and it must therefore be admitted that selection on the basis of risk factors can not prevent transfers of some women during labour at home (or in a 'clinic' outside a hospital) to a well-equipped obstetric hospital. In the Dutch 'Wormerveer-study' (Table 1), however, it was shown that after careful selection, in only 6·5% of the cases did symptoms or signs occur during labour which made it advisable to transfer the woman to a hospital (Kloosterman 1983).

Whereas there is agreement in both countries that labour is only normal when it is over, the difference is, that in The Netherlands the impossibility of predicting a normal outcome is accepted by relying on transport during labour.

When comparing the situation in Denmark and The Netherlands other factors should be taken into account. After a home delivery, but

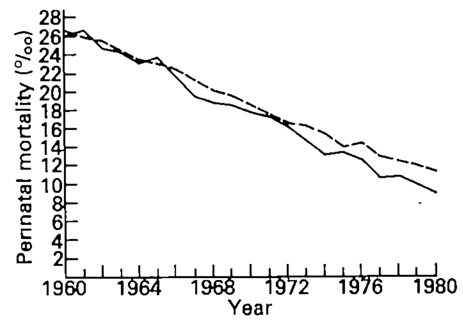

Fig. 3. Perinatal mortality. See Fig 1.

also after a 'policlinic delivery' (where mother and baby are sent home a few hours after the birth in hospitals; short-short-stay) in The Netherlands, the family is assisted by a professional person who spends 8 h a day at home during 7 days. In Denmark the new mother has only a few short visits by the midwife and the nurse (sundhedsplejersken). She can have additional help, but she must pay for it and if the family has a medium income or more this is very expensive.

A Dutch study (Lapré 1972) showed that the system with home confinements and professional assistance by a 'maternal-home-help-organization' (MHH) appeared to be less expensive than a system with total hospitalization. This study was performed at a time when the percentage of home deliveries was more than 50%. If the number of home confinements becomes considerably lower the point will come when an organization such as the MHH, which is heavily subsidised, will be too expensive. In 1984 more than 60% of all young mothers spent their lying-in period at home (34% home confinements and 30% 'policlinic deliveries'). This makes the organization of the MHH worthwhile. If a country with a large number of obstetric hospitals would contemplate the reintroduction of a system similar to that now operating in The Netherlands it would, at least initially, require considerable extra expense.

Although financial aspects may have been a consideration in Denmark, it has not been shown in Danish studies that a policy of almost total hospitalization is less expensive than a policy in which a substantial proportion of births take place at home.

The very low number of home deliveries in Denmark does not reflect women's views on the issue. Howitz & Ussing (1978) asked 5240 women whether they would prefer to give birth in an institution or at home and 16·5% preferred to give birth at home. Although the study sample may not represent the opinion of pregnant Danish women at the present time, the difference between the actual percentage of home-confinements (1%) and the percentage found in that study (16·5%) is very striking. Women who begin by wanting a home confinement are presumably dissuaded by a combination of professional, financial and logistic factors.

Perinatal mortality rates have improved in both countries. The improvement is greater in Denmark, however, and this reflects a greater improvement in the early neonatal death rate than in The Netherlands. The improvement in the stillbirth rate was almost identical in the two countries.

A low early neonatal death rate indicates a safe environment for the newborn at the time of birth and the first days of life. The greater improvement in Denmark in the early neonatal death rate demands an explanation because it could be that the Danish organization is safer than the Dutch. Insufficient referral of high-risk cases in The Netherlands may be a partial explanation (van Alten & Eskes 1983).

This would mean that it was not the phasing out of 'planned' home confinements (Murphy *et al.* 1984) in Denmark which led to the better results, but another change in obstetric organization which occurred at the same time, that is phasing out obstetric care in small 'clinics' and hospitals without facilities for handling real pathology in obstetric and neonatal care. A recent study from New Zealand (Rosenblatt *et*

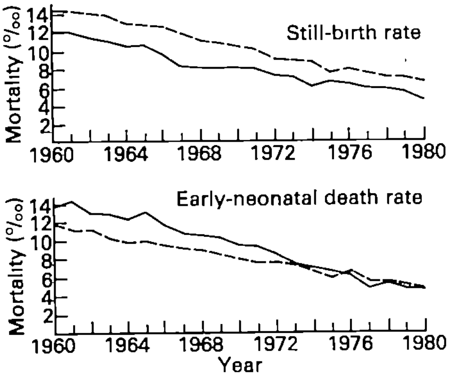

Fig. 4. Still-birth- and early neonatal-death-rate See Fig. 1.

Table 1. The 'Wormerveer-Study' (1970–1977)

Place of birth	Births		Perinatal mortality	
	n	(%)	*n*	rate/1000
Hospital, after referral of the mother during pregnancy	778	(16·1)	32	41·1
Hospital, after referral of the mother during labour	316	(6·5)	6	19·0
At home or in maternity unit	3741	(77·4)	6	1·6
Total	4835	(100·0)	44	9·1
Total booked for home or maternity unit delivery	4057	(83·9)	12	3·0

al. 1985) shows that when there is an ideal regionalized obstetric system with cautious antenatal controls, birthweight-specific perinatal mortality rates (> 1500 g) are lowest in small 'low technology' maternity units, where low-risk women are accepted and cared for by general practitioners and midwives. This situation is comparable with The Netherlands where low-risk pregnancies are accepted at home, also with good results. The situation is quite different where small hospitals and clinics accept high-risk pregnancies, without a sufficient capacity to deal with complications, and emphasizes the importance of selection for risk.

The methodological problems in the estimation of the risk associated with different places of delivery have recently been discussed by Murphy *et al.* (1984). Those problems, and the heterogeneity of the groups giving birth at alternative places, will probably obstruct an unbiased analysis of differing systems of care.

It is evident that Denmark had to pay for the better perinatal results with a high number of interventions, and there seems no doubt that more hospitalization induces a higher chance of intervention.

This has been shown by comparing low-risk pregnancies delivered in specialized obstetric units with comparable pregnancies delivered in non-specialized units (Klein *et al.* 1983; Barton *et al.* 1980). When high-risk and low-risk pregnancies are treated in the same unit the principles of intervention are easily used on the low-risk pregnancies with less criticism. It could be argued that the Danish medical students and midwives are trained to look for the complications that is to be 'crisis-oriented', instead of looking for the normal course of labour and delivery.

It is unlikely that the attitude of the Danish obstetricians will change towards advocating more home confinements to reduce the number of interventions, but they have recognized and discussed the problem. One of the ways out of the situation may be the establishment of an 'alternative birth centre' (Klein *et al.* 1983; Goodlin 1980) which has proved to be effective in the United States and Great Britain. A Danish study has begun to examine this possibility.

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I wish to thank Professor Dr J. Falck Larsen and Professor Dr G. J. Kloosterman for their encouraging interest in this subject during my stay in Denmark and thereafter.

This publication is the result of a study suggested by Professor Dr G. J. Kloosterman and carried out in Denmark 1981.

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Regional perinatal mortality and regional hospitalization at delivery in The Netherlands

P. E. TREFFERS, R. LAAN

Summary. In The Netherlands 34–35% of all deliveries still take place at home, but with considerable regional differences. A study was made of the relation between the perinatal mortality rate and the percentage of hospital deliveries in the 11 provinces of The Netherlands, in municipalities divided into groups according to the number of inhabitants, and in the 17 cities with more than 100 000 inhabitants. No relation could be demonstrated between the regional percentage of hospital deliveries and the regional perinatal mortality rate. The proportion of hospital delivery appears not to be a major factor determining the regional perinatal mortality rate in the current system of obstetric care in The Netherlands.

In The Netherlands, in contrast to most other European countries, a considerable number of deliveries still take place at home. Since 1945 hospitalization at delivery has steadily increased, but not until 1971 did the proportion of hospital deliveries exceed 50%. Since 1978 the percentage of home deliveries has stabilized at 34–35%, although large regional differences exist. In some cities (Amsterdam. Leiden, Nijmegen) the number of home deliveries has slightly increased in recent years; in other regions, especially those with a relatively low rate of hospitalization, hospital deliveries are still increasing slightly. The Dutch system of obstetric care, based on selection related to risk factors during pregnancy and delivery, is subject to much debate. In particular, whether or not home deliveries in low-risk pregnancies are justified and safe has not been agreed. National figures for perinatal mortality have decreased during the last decades, the perinatal mortality rate per 1000 was 13·9 in 1975, 11·9 in 1979 and 10·0 in 1982.

In this article we wish to report on the regional differences in hospitalization at delivery in relation to regional perinatal mortality figures.

Subjects and methods

Data on births, perinatal mortality and place of birth are registered by the CBS (Central Bureau of Statistics 1980–1983). Births are defined as live births irrespective of gestational age, and stillbirths from 28 weeks of gestation. Perinatal deaths are all stillbirths from 28 weeks of gestation, and all neonatal deaths up to 7 days after birth. The percentage of hospital deliveries per region and data on perinatal mortality are given for a period of 4 years (1979–1982). With two exceptions the minimum number of births used to calculate perinatal mortality rates was 5000.

Births and perinatal deaths are notified in the municipality where the birth or death took place, but are registered by the CBS in the municipality of residence of the mother. Statistical calculations were performed using the Spearman rank correlation test

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Results

Table 1 shows the percentage of hospital deliveries and perinatal mortality figures in the 11 provinces of The Netherlands. Hospitalization at delivery varied from 49·2% to 75·7%. In the last columns perinatal mortality rates and ranking order by perinatal mortality are given (low numbers correspond with low perinatal mortality rates). There was clearly no relation between the degree of hospitalization in the province and the perinatal mortality rate (r=0·0, P=1).

Table 2 shows the percentage of hospital deliveries and perinatal mortality in municipalities divided into groups according to the number of inhabitants. Hospitalization at delivery was clearly correlated with the degree of urbanization: the percentage of hospital deliveries was low in smaller communities and high in cities with more than 100 000 inhabitants but no similar relation could be observed between perinatal mortality rate and size of municipalities.

Perinatal mortality was certainly not lower in larger cities with a high degree of hospitalization at delivery.

The totals of births and deaths in the Tables 1 and 2 are slightly different, because in Table 1 a small new polder in the former Zuiderzee, not yet assigned to a province, has not been included. With this exception both tables contain data from The Netherlands as a whole

In Table 3 the percentage of hospital deliveries and perinatal mortality figures are shown for all 17 cities with more than 100 000 inhabitants. Hospitalization at delivery in those cities varied considerably, from 50·5% to 95·7%. Perinatal mortality rates were lowest in Leiden (10·0) and Groningen (10·1). Perinatal mortality rates in some of the largest cities, The Hague (13·4) and Amsterdam (12·8), were among the highest of the country.

In the last column the ranking order by peri-

Table 1. Percentage of hospital deliveries in the provinces of The Netherlands, and perinatal mortality 1979–1982 The provinces are arranged according to the percentage of hospital deliveries, in the last column the ranking order by perinatal mortality rate is given

			Perinatal mortality		
Province	% Hospital deliveries	Number of births	No of deaths	Rate/1000	Ranking order
Noord-Holland	75·7	106 591	1167	11·0	7
Limburg	70·7	48 874	589	12·1	11
Zuid–Holland	67·6	155 630	1677	10·8	4
Utrecht	66·8	45 884	484	10·6	2/3
Zeeland	60·3	18 169	201	11·1	8
Gelderland	58·9	86 537	918	10·6	2/3
Overijssel	58·5	57 106	602	10·5	1
Groningen	56·4	27 092	296	10·9	5/6
Drenthe	53·2	20 747	246	11·9	10
Noord-Brabant	52·2	105 605	1183	11·2	9
Friesland	49·2	32 772	356	10·9	5/6

Table 2. Percentage of hospital deliveries in municipalities arranged according to the number of inhabitants, and perinatal mortality 1979–1982

			Perinatal mortality	
Number of inhabitants	% Hospital deliveries	Number of births	No of deaths	Rate/1000
< 5000	52·2	42 516	499	11·7
5000–20 000	53·3	234 218	2412	10·3
20000–50 000	60·6	174 589	1850	10·6
50000–100 000	69·4	95 607	1057	11·1
>100 000	77·4	163 685	1934	11·8

Table 3. Percentage of hospital deliveries in cities with >100 000 inhabitants, and perinatal mortality 1979–1982 The cities are arranged according to the percentage of hospital deliveries, in the last column the ranking order by perinatal mortality rate is given

City	% Hospital deliveries	Number of births	Perinatal mortality		Ranking order
			No of deaths	Rate/1000	
Enschede	95·7	6908	86	12·5	13
Haarlem	89·4	6529	83	12·7	14
Utrecht	89·3	9982	111	11·1	7/8
Leiden	85·0	5008	50	10·0	1
Nijmegen	81·6	6345	68	10·7	6
The Hague	81·6	18 956	253	13·4	17
Groningen	80·7	6763	68	10·1	2
Arnhem	80·6	5931	63	10·6	4/5
Amsterdam	80·5	30 730	393	12·8	15
Zaanstad	79·8	6469	72	11·1	7/8
Maastricht	79·3	4249	49	11·5	10
Rotterdam	78·2	24 631	286	11·6	11
Dordrecht	67·1	5630	63	11·2	9
Eindhoven	58·4	8411	102	12·1	12
Breda	56·0	4820	49	10·2	3
Tilburg	55·6	7490	99	13·2	16
Apeldoorn	50·5	6626	70	10·6	4/5

natal mortality rate is given (low numbers correspond with low perinatal mortality rates). There was clearly no relation between the degree of hospitalization at delivery in the cities and perinatal mortality rate (r=0·18, P=0·5).

Discussion

It is obvious that, although considerable regional differences exist in the degree of hospitalization at delivery, there is no relation between regional hospitalization and regional perinatal mortality rate. The results are in accordance with those of earlier investigations (Treffers 1978).

The reliability of perinatal mortality data has been questioned in recent years From research in the city of Amsterdam it became clear that registration by the CBS is practically 100% accurate, but that the notification of cases of perinatal mortality by individual physicians is not. The underreporting turned out to be 14·0% (Doornbos & Nordbeck 1985). Among cases not notified the incidence of infants with very low birthweight (<1000 g) and very short gestational age (<28 weeks) was relatively high. Underreporting was also shown to be more frequent after perinatal deaths in infants of immigrants from Mediterranean countries. Because no exact data are available about underreporting in other regions, no conclusive evidence can be given about the influence of registration procedures on regional perinatal mortality figures. There is no indication, however, of large differences in notification between regions. Only a small minority of all registered perinatal deaths occurs at home (in Amsterdam 5%, whereas nearly 20% of all deliveries take place at home). This is not unexpected because patients with complications during pregnancy or delivery are usually referred to a hospital. No data are available, however, about underregistration or deaths at home compared with hospital deliveries. As notification of a perinatal death is obligatory before permission to bury the infant is granted, it might be more troublesome to avoid notification after a perinatal death at home, because disposing of a dead infant, without a formal burial, is more difficult at home than in a hospital

Figures on perinatal mortality are not standardized for maternal age and parity. There are not large differences in the number of children per family and in the age of the mothers between indiginous Dutch people of different regions. Considerable differences, however, exist between Dutch and immigrant families. The most important immigrant groups are from

Surinam and the Dutch Antilles, from Morocco and Turkey. High maternal age and high parity occurs more often in these immigrant groups than in the Dutch population. These ethnic minorities are concentrated in larger urban centres In Amsterdam in recent years, one third of all infants are born of families originating from foreign countries. Perinatal mortality in these immigrant populations is higher than in the indiginous Dutch. The degree of hospitalization at delivery is also different. In Amsterdam 40–50% of Moroccan and Turkish women give birth at home. By contrast 95% of the women of Surinam origin give birth in hospital, yet they have the highest perinatal mortality rate of all ethnic groups (Doornbos & Nordbeck 1985).

While the degree of hospitalization at delivery appears not to be a major factor determining the regional perinatal mortality rate in The Netherlands, it must be stressed that this conclusion should be seen against the background of the Dutch system of obstetric care characterized by competent midwives, maternity home aids assisting the midwives during delivery and in the post-partum period, selection of high- and low-risk pregnancies, and a good ambulance service in this densely populated country, allowing, in cases of emergency, the transportation of a woman in labour to a nearby hospital with minimal delay (Keirse 1982; Kloosterman 1984).

The conclusion may not be valid in countries or regions where these conditions are not fulfilled. Moreover, the question whether an obstetric system comprising home deliveries is justified cannot be answered by perinatal mortality figures alone; other criteria, including infant morbidity, must also be taken into account.

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Perinatally related wastage—a proposed classification of primary obstetric factors

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Summary. Adapting Sir Dugald Baird's concept of primary obstetric causes of perinatal mortality, a revised clinico-pathological classification has been evolved to take account of new knowledge and developments, and to direct attention to potentially avoidable deaths and to where intensified efforts and investigation are needed. Categories highlighting the importance of intrauterine growth retardation, unexplained intrauterine death and spontaneous premature labour have been introduced, intrapartum hypoxia is separated from birth trauma, and infection again has its own category. Regular perinatal audit at one obstetric hospital, since 1979, has shown that the new system provides a workable and useful means for classifying not only perinatal deaths, but also late abortions, late neonatal deaths and perinatally related infant deaths. The rate of total perinatally related wastage, defined in this way, was almost twice that for perinatal mortality (22·8 compared with 11·9 per 1000 births). The former is advocated as a more realistic index for the audit of perinatal care. The revised and extended system is put forward as a contribution to the current debate on classifying and reporting such wastage, in the hope that it may be tested as a model for regional as well as hospital surveys.

Perinatal mortality should be classified in several ways—epidemiological, by time in relation to birth (stillbirths and first week neonatal deaths; or antepartum, intrapartum and postpartum), obstetric, neonatal and pathological. Each has its own value and complements the others. For the obstetrician, documentation of the primary event or factor that initiated the process or sequence of events leading to each death is of paramount importance. This is the basis of the well known clinico-pathological classification devised in Aberdeen, and first described by Baird *et al.* (1954). It was developed further by Baird & Thomson (1969) and, with additional small modifications, remains in use particularly in Scotland where surveys of perinatal mortality during the years 1977–1981 have been reported (McIlwaine *et al* 1979, 1985)

Any clinico-pathological classification of perinatal wastage must be revised from time to time to take into account new knowledge and diagnostic methods, and to highlight new directions in which it has become possible to effect improvements or which require intensive study. Thus for example, Baird's 'mature unknown'

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and 'premature unknown' groupings, renamed 'normal birthweight' and 'low birthweight' in the Scottish surveys, are now too unspecific as primary categories, and it is no longer helpful to group together (as low birthweight) deaths of very premature liveborn babies and the death *in utero* of fetuses weighing less than 2·5 kg. Intrauterine growth retardation (IUGR) has come to be recognized as an important, ultrasound-detectable condition sometimes leading to deaths that might be avoidable by appropriate monitoring and intervention, and therefore it should now have its own primary category.

Three other potentially avoidable or treatable causes of perinatal and related mortality should also be categorized separately. These are birth trauma and intrapartum hypoxia, which are preventable by different means and can be distinguished from each other by evidence from intrapartum monitoring and autopsy; and infection, confirmed by histopathology and/or microbiological investigation, for which a separate category was introduced into the Aberdeen classification (Baird & Thomson 1969) but which reverted to being one of a miscellaneous group of 'other causes' in the Scottish surveys.

The customarily defined temporal limits for perinatal mortality, namely 28 weeks gestation and the end of the first week of life, have been made obsolete by the results of modern intensive neonatal care. Thus, it is no longer uncommon for babies born before 28 weeks gestation to survive, while other babies live through the first week, only to die later as an eventual result of their prematurity at birth or from the effects of other perinatal complications.

For these reasons, while wishing to retain the important principles of Baird's classification, we believe that some of its primary categories should be revised and that the range of perinatal wastage should be extended to include late abortions and all neonatal and perinatally related infant deaths, rather than only stillbirths and first week deaths A revised and extended obstetric classification of 'total perinatally related wastage' (TPRW) was therefore introduced at the Queen Mother's Hospital. We present the results of applying this system of classification to TPRW at the hospital during the 4 years 1979–1982 as a model from which to argue the case for reviewing and reporting pregnancy wastage along these or similar lines, in both single hospital audits and area or regional surveys.

Methods and definitions

Total perinatally related wastage (TPRW) is defined as including all late abortions, except terminations of pregnancy for fetal abnormalities, all perinatal deaths, all late neonatal deaths (during the second, third and fourth weeks of life) and all infant deaths (between 1 month and 1 year of life) due or partly due to a primary perinatal complication or its treatment Late abortions are defined as those occurring after 20 completed weeks gestation, the gestational age being determined from the menstrual history and particularly from ultrasound measurements of the fetus made early in pregnancy. Perinatal deaths are defined, in the standard manner, as stillbirths (at 28 weeks or more) and deaths during the first week of life.

Information was obtained from the clinical records and postmortem examination reports on all late abortions and stillbirths at the Queen Mother's Hospital during the 4 years (1979–1982), and on neonatal and infant deaths of babies born in the hospital during this period. Terminations of pregnancy for fetal abnormality were excluded from TPRW; they are separately recorded and declared with terminations performed earlier in pregnancy for the same indication. Late therapeutic abortions for other medical or obstetric indications were included in TPRW, as were late induced abortions following fetal death and all late spontaneous abortions. All neonatal deaths were included, but infant deaths unrelated to any perinatal factor were excluded; for the purposes of this study, the sudden infant death syndrome ('cot death') was not deemed to be perinatally related.

The Glasgow post-perinatal mortality survey (Arneil *et al.* 1982) provided a valuable means for ascertaining deaths, within the first year of life, of babies who had been discharged from the hospital. The majority of these deaths occurred in the adjacent Royal Hospital for Sick Children, but when necessary, relevant information was obtained from other hospitals.

Based on the information collected, the revised and extended classification (categories defined below) was applied to each perinatally related loss. For comparison with this system, each perinatal death was also categorized by the 'final' version of the Aberdeen classification (Baird & Thomson 1969) and by the modified version used in the Scottish surveys (McIlwaine *et al.* 1979, 1985).

Proposed classification of TPRW

(1) *Spontaneous preterm (SP).* Deaths attributed to immaturity (or its complications) of normally formed, appropriately grown babies born before 37 weeks gestation as a result of spontaneous labour, and spontaneous late abortions other than those known to have occurred some time after death of the fetus. The following subcategories, some similar to those used in the Scottish surveys, are noted: (a) *multiple pregnancy* which, for purposes of classification, takes precedence over any other co-existent factors listed as subcategories; (b) *previous bleeding,* defined as a history of one or more episodes of vaginal bleeding not leading immediately to spontaneous abortion or preterm labour; (c) *previous spontaneous rupture of membranes,* when this precedes the onset of spontaneous abortion or preterm labour by more than 12 h; (d) *incompetent cervix,* when convincing evidence, from the previous obstetric history and/or the state of the cervix, suggests the likelihood of cervical incompetence as a predisposing factor, whether or not a cervical suture has been inserted; (e) *other* (e.g. uterine malformation); (f) *idiopathic.*

When preterm labour or abortion occurs as a consequence of another primary cause (e.g. when it follows unexplained fetal death or placental abruption) the loss is classified in the appropriate primary category (see below)

(2) *Intrauterine growth retardation (IUGR).* All otherwise unexplained losses of normally-formed fetuses or newborns with birthweights which are either (a) less than the 5th centile for gestational age (at the time of fetal death or livebirth) based on the tables for Scottish babies corrected for sex but not for parity (Forbes & Smalls 1983) (an arbitrary extrapolation of the 5th centile into the second trimester was used to define IUGR for late abortions); or (b) are above the 5th centile but repeated ultrasound measurements have already shown arrest or retardation of growth before death *in utero.*

(3) *Unexplained intrauterine death (UXIUD).* Stillbirths and late abortions of normally formed fetuses without IUGR are classified in this primary category if fetal death is known to have preceded labour or abortion, in the absence of any other primary complication.

Categories 1, 2 and 3 together correspond, in the main, to the premature unknown/low birthweight and mature unknown/normal birthweight categories of the Aberdeen and Scottish systems.

(4) *Trauma (TR).* Stillbirths and deaths of normally formed babies, of at least 1·5 kg birthweight, with evidence of lethal trauma at autopsy (usually tentorial tears). In these circumstances this category applies even when labour and delivery were not complicated by mechanical difficulty Traumatic deaths of babies weighing less than the arbitrary limit of 1·5 kg at birth are usually designated as spontaneous preterm (or less commonly, if appropriate, as IUGR).

(5) *Intrapartum asphyxia (IPA).* Stillbirths and deaths of normally formed babies, preceded by evidence of intrapartum hyoxia (e.g. monitored fetal heart rate changes and fetal scalp blood acidosis) and confirmed by the demonstration of hypoxic changes at autopsy. As with deaths from birth trauma, 1·5 kg is used as an arbitrary lower limit of birthweight for inclusion in this category.

Categories 4 and 5 correspond to, and replace, the single category of 'trauma' in the Baird classification, but, as in Baird's system, an association with umbilical cord complications, breech delivery or operative delivery (other than breech) is noted as a subcategory, if appropriate.

(6) *Hypertension (HYP)* Losses attributed to pre-existing or pregnancy-induced hypertension, or to its complications or treatment. The nature of the hypertensive disorder is cited as a subcategory (e g. The pre-eclampsia, renal or essential hypertension).

(7) *Maternal disease (MD).* Losses attributed to any medical or surgical disorder in the mother, or to its complications or treatment, excluding hypertensive disorders.

Categories 6 and 7 correspond to the Baird categories labelled 'toxaemia' and 'maternal disease', except that we classify pre-eclampsia and its complications with all other hypertensive disorders in a single primary category, leaving only non-hypertensive disorders to be categorized as maternal disease. When a hypertensive or other maternal disorder is, or seems to be, the factor initiating a chain of events leading to the immediate cause of death the loss is attributed to the primary disorder. As examples, deaths from placental abruption complicating hypertensive states and deaths from immaturity following preterm delivery undertaken in the management of severe pre-eclampsia are classified as due to the hypertension.

(8) *Antepartum haemorrhage (APH).* In

attributing losses to antepartum haemorrhage, its accepted definition is extended beyond the traditional early limit (28 weeks) to 20 completed weeks gestation. The traditional subcategories—placental abruption, placenta praevia, and antepartum haemorrhage of undetermined origin—are used, but when placental abruption occurs as a complication of a hypertensive disorder the loss is attributed to the hypertension.

(9) *Fetal abnormality (FA).* Losses attributed to major fetal abnormalities, excluding late terminations of pregnancy undertaken because of the abnormality (these are declared separately along with therapeutic abortions carried out earlier in pregnancy for the same indication). As in the other systems, we use subcategories for chromosomal disorders, for non-chromosomal abnormalities of the different systems (e.g. central nervous, cardiovascular and renal), for multiple malformations, and for non-chromosomal metabolic errors unassociated with major structural abnormalities. In each case a judgement is also made as to whether or not the abnormality was detectable, by standard prenatal diagnostic methods, in time to permit therapeutic abortion. Detectability in this sense is unrelated to whether or not the patient reported for care sufficiently early in her pregnancy, whether or not specialised prenatal diagnosis was indicated, offered and accepted, and it is also unrelated to whether or not the fetal anomaly was actually detected *in utero*.

(10) *Haemolytic disease (HD).* Losses attributed to haemolytic disease, or to its complications or treatment, are placed in three subcategories—rhesus incompatibility, other feto-maternal blood group incompatibilities (e.g. Kell), and the haemoglobinopathy of alpha-thalassaemia.

(11) *Infection (INF).* Losses attributed to bacterial, viral, fungal or protozoal infections occurring as primary factors, including intrauterine or neonatal deaths with evidence of chorioamnionitis or congenital pneumonia preceding membrane rupture, and also deaths from infection of newborn infants not already judged to be at significant risk from another primary cause; but excluding deaths from infection complicating other primary factors (e.g. 'spontaneous preterm' is the appropriate category when fetal necrotizing enterocolitis or septicaemia complicates treatment of very premature babies). Pathological evidence of infection is required, and the organisms responsible are cited as specific subcategories.

(12) *Other.* Losses attributed to miscellaneous primary causes other than those defined above. This category includes hydrops fetalis not caused by haemolytic disease.

Results

During the 4 years 1979–1982 there were 13 446 total births with 307 perinatally related losses comprising 94 late abortions, 67 stillbirths, 93 first week neonatal deaths, 27 later neonatal deaths and 26 perinatally related infant deaths

The perinatal mortality rate was 11·9 per 1000 births. Table 1 shows how the 160 perinatal deaths are classified in the 11 causal groups of the Aberdeen system and in the nine groups used in the Scottish surveys, and how they are redistributed among the 12 primary categories of our proposed classification. For deaths due to Antepartum Haemorrhage and Fetal Abnormality (termed Fetal Deformity in the Scottish system) there are no changes in the allocation of cases between the three systems.

Of 45 losses in the premature unknown/low birthweight grouping, only 27 neonatal deaths remain in our chief corresponding category—i.e. Spontaneous Preterm, eight stillbirths reclassify as due to IUGR, and 10 others as due to Unexplained Intrauterine Death, as do five from the mature unknown/normal birthweight grouping. The other three normal birthweight deaths and two attributed to trauma by the rules of the other classifications were shown by autopsy to have been caused by acute hypoxia and are recategorized accordingly to Intrapartum Asphyxia. Trauma remains the correct category for three neonatal deaths caused by tentorial tearing and intracranial haemorrhage.

The eight deaths in the toxaemia group remain in the corresponding category of Hypertension which also includes seven deaths attributed to hypertensive disorders that preceded pregnancy (classified as Maternal Disease in the Aberdeen and Scottish surveys), leaving only three deaths in our primary category of Maternal Disease (diabetes; leukaemia; systemic lupus erythematosis).

Five of 10 deaths classified in the Scottish system as due to other causes could confidently be attributed to Infection and were therefore reallocated to this category (in which they would also be assigned in the final version of the Aber-

Table 1. Classification of primary causes of 160 perinatal deaths

Aberdeen classification (Baird & Thomson 1969)		Scottish surveys	Proposed classification		(Abbreviation)
Premature unknown		— Low birthweight	45 — 27 → Spontaneous preterm	27	SP
			8 → Intrauterine growth retardation 10	8	IUGR
Mature unknown		— Normal birthweight	8 — 5 → Unexplained intrauterine death	15	UXIUD
			3 → Intrapartum asphyxia 2	5	IPA
Mechanical		— Trauma	5 — 3 → Trauma	3	TR
Toxaemia		— Toxaemia	8 → Hypertension 7	15	HYP
Maternal disease		— Maternal disease	10 — 3 → Maternal disease	3	MD
Antepartum haemorrhage		— Antepartum haemorrhage	13 → Antepartum haemorrhage	13	APH
Malformation		— Fetal deformity	52 → Fetal abnormality	52	FA
Serological incompatibility		— Rhesus	9 → Haemolytic disease 1	10	HD
Infection	5	Other	5 → Infection	5	INF
Miscellaneous defined causes	5		10 — 4 → Other	4	Other
Unclassified (inadequate information)	0				
			160	160	

The arrows show how the deaths classified in each category of the Aberdeen system and the Scottish modification (on left) are distributed on reclassification by the proposed system (on right).

deen classification (Baird & Thomson 1969)). The death of a hydropic baby due to alpha-thalassaemia was transferred on reclassification to Haemolytic Disease, leaving only four due to Other causes.

TPRW

The rate for TPRW, at 22·8 per 1000 births, was virtually twice as high as the perinatal death rate, and the losses in each primary category of the proposed classification are shown in Table 2. In addition, 31 late therapeutic abortions were performed because major fetal abnormalities had been detected; these, together with 24 therapeutic abortions before 20 weeks for the same indication, give a total of 55 pregnancies terminated for fetal abnormality which are not included in TPRW.

More than half the TPRW was in the Spontaneous Preterm (29%) or Fetal Abnormality (26%) categories, the former being the primary cause in 39% of all TPRW if congenital abnormalities are excluded. The next most frequent primary cause was Antepartum Haemorrhage (12%), followed by Hypertension (7·5%), Unexplained Intrauterine Death (7%) and IUGR (5%). Infection and Haemolytic Disease were each responsible for 4% of TPRW, Trauma and Intrapartum Asphyxia were together responsible for less than 3%, and Maternal Disease for less than 2%.

In all except five of the 90 losses categorized as Spontaneous Preterm there were predisposing factors, of which multiple pregnancy (17 cases), previous vaginal bleeding (25 cases), spontaneous membrane rupture (20 cases) and probable cervical incompetence (14 cases) were the most common. Twenty of the deaths in this category (22%) occurred after the first week of life,

Table 2. Classified total perinatally related wastage (TPRW)

Cause	Late abortions	Stillbirths	Early neonatal deaths	Late neonatal deaths	Perinatally related infant deaths	TPRW
Spontaneous preterm	43	—	27	16	4	90
Intrauterine growth retardation	7	6	2	—	—	15
Unexplained intrauterine death	6	15	—	—	—	21
Intrapartum asphyxia	—	—	5	—	—	5
Trauma	—	—	3	—	—	3
Hypertension	4	12	3	2	2	23
Maternal disease	2	1	2	—	—	5
Antepartum haemorrhage	19	9	4	2	2	36
Fetal abnormality	5	16	36	5	17	79
Haemolytic disease	4	5	5	—	—	14
Infection	4	1	4	1	1	11
Other	—	2	2	1	—	5
Totals	94	67	93	27	26	307

including four infant deaths at 1–5 months of age.

Seven fetal deaths attributed to IUGR and six examples of Unexplained Intrauterine Death led to spontaneous or induced abortion, so that when these two categories are combined more than one-third of the losses were not, by definition, perinatal deaths.

The 15 perinatal deaths, four later deaths and four late abortions attributed primarily to Hypertension comprised 13 due to pre-eclampsia or eclampsia (one case) and 10 resulting from pre-existing hypertensive disease. Placental abruption, complicating hypertension, was the immediate cause of three stillbirths in this category.

Thirty of the 36 losses attributed primarily to Antepartum Haemorrhage were caused by placental abruption There were more late abortions (19) than perinatal deaths (13) in this category, and one of four deaths after the first week of life occurred at the age of 18 weeks, as a result of complications of immaturity and its treatment.

Six of the 79 mothers, whose babies died from major Fetal Abnormality, had been transferred from elsewhere for specialized prenatal diagnosis Cardiac malformations were the most common (23), followed by chromosomal anomalies, neural tube defects and multiple malformations in almost equal proportions, these four main subcategories making up four-fifths of all the lethal abnormalities Malformations accounted for the majority of perinatally related infant deaths during the 4-year period (17 out of 26, including 10 deaths due to cardiac anomalies). Thirty-one (39%) of the fetal abnormalities were considered to have been detectable by established methods of prenatal diagnosis, but usually in these cases the patient had attended or had been referred too late to offer the option for selective therapeutic abortion, or she had decided against this course During the 4 years, 55 therapeutic abortions were carried out for detected fetal abnormalities (not included in TPRW); in all but five of these the abnormality was either a neural-tube defect (38 cases) or a chromosomal anomaly (12 cases).

The 14 losses attributed to Haemolytic Disease included 12 due to rhesus incompatibility, among which there were three abortions following fetal death soon after intrauterine blood transfusion, and a similar post-transfusion abortion was the outcome in a patient with Kell iso-immunization. Seven of the patients had been transferred from other obstetric units. The death of the hydropic baby with alpha-thalassaemia was also included in this category.

Infection *in utero* caused four late abortions and a stillbirth, and neonatal infection caused six further deaths. Group B beta-haemolytic streptococci and cytomegalovirus were each responsible in three cases.

Of the five deaths attributed to Other causes, it is noteworthy that large transplacental (feto-maternal) haemorrhages were shown to be the cause of two stillbirths and one neonatal death.

Discussion

There is unlikely to be argument with the view that detailed scrutiny of each perinatal death and identification of its cause are essential, and that local, regional and national audits of perinatal wastage are required to identify deficiencies in the provision of care, to focus attention where improvements are already possible, and to indicate how new developments or knowledge may be expected to lead to further advances. While sharing the scepticism of Wigglesworth (1980) about the tendency 'to search for even more comprehensive means of collecting and analysing perinatal data in the hope that eventually some inspired analysis will allow complete definition of the causes and nature of perinatal mortality', with other colleagues we believe that some existing systems of classification are too simplified to be of much value on their own, while others have been overtaken by new advances and by new knowledge and opportunities. While also understanding the need for complementary epidemiological, pathological and paediatric classifications, we recognize the continued primacy of Baird's concept that the obstetric classification should categorize the identified, or most likely, primary factors or complications causing death or initiating the sequence of events leading to it. Baird & Thomson (1969) described the fundamental problem as 'deciding which out of several possible 'causes' of death is the primary feature towards which efforts at prevention should be directed'. To exploit new developments any classification must be updated from time to time by redefining categories and introducing new ones when appropriate. Indeed, Baird and his colleagues themselves revised and refined some of their descriptions and definitions, e.g. infection and serological (Rh) incompatibility, both originally included among 'other causes', were given their own separate categories, and the rubric of Trauma was changed to Mechanical to make clear the inclusion of deaths attributed to mechanical obstruction during labour, even in the absence of postmortem evidence of birth trauma (Baird & Thomson 1969).

It was in the belief that a major revision of primary aetiological categories was overdue, and that extension beyond the presently defined temporal limits of perinatal mortality was also required, that the classification described here was devised.

The classification in its original form was introduced 7 years ago, but has itself been revised in the light of experience, and it now provides a workable and useful system on which monthly and annual reviews of perinatal mortality and TPRW are based. At first, ascertainment of deaths up to one year following birth was almost certainly very incomplete, but the Glasgow post-perinatal mortality survey (Arneil *et al* 1982; Arneil 1983) has, we believe, enabled us to make this nearly complete during the 4 years reviewed, and has shown that this is possible on an area basis. A few such deaths occurring elsewhere, as a result of families moving from Glasgow, may of course be unknown to us. At the other end of the spectrum of TPRW, the already established practice of submitting abortuses for postmortem examination made it possible to include these from the start, and the midpoint of pregnancy (20 weeks) was chosen as a convenient arbitrary limit. By that stage, most of our patients have booked for care and confinement, and they will usually be admitted to our hospital, rather than to a gynaecological unit, if they abort subsequently. The results described confirm that abortions after 20 weeks gestation show the same pattern of causes and predisposing factors as do early stillbirths. We therefore prefer the 20 weeks' limit to using either the registration limit of 22 weeks (or the equivalent birthweight of 500 g, or crown-heel length of 25 cm) proposed by a standing committee of the International Federation of Gynecology and Obstetrics (FIGO 1982), or the viability limit of 24 weeks recently recommended in the British representative Report on Fetal Viability and Clinical Practice (1985). Data relating to late abortions are often very incomplete, but we believe this supports, rather than contradicts, the argument to include this important component of perinatally related wastage in the system of audit and to ask all concerned to provide the necessary information.

In any system of classification there will be occasions when choices have to be made between two possible primary categories, and for consistency it is important that clear guidelines should be established and followed. Thus, when a baby weighing less than 1·5 kg at birth dies from intracranial or other trauma, we classify the loss as due primarily to immaturity (e.g. Spontaneous Preterm). This rule is similar to that used in the Aberdeen and Scottish systems, by which traumatic deaths of babies weighing less than 1·815 kg (4 pounds) are classified as premature unknown/low birthweight, but we consider our arbitrary dividing line (1·5 kg) as more realistic, and it has the additional merit of being consistent with the growing practice of reporting mortality and survival rates in 0·5 kg birthweight bands. Baird's practice is followed in attributing to Hypertension any death from placental abruption occurring as a secondary complication of the hypertensive disorder. Following the same principle, when lethal infection occurs as a complication of spontaneous premature membrane rupture the appropriate primary category is Spontaneous Preterm, but if the evidence suggests that infection preceded and thus probably caused rupture of the membranes the correct label is Infection

It is the local practice to define the small-for-dates fetus as having a birthweight on or below the 5th centile for gestational age, and for classification purposes otherwise unexplained deaths of such babies have been categorised as due to IUGR, as have those of babies with birthweights above the 5th centile but in which unequivocally retarded, or arrested, intrauterine growth has been demonstrated by serial ultrasound measurements. By either of these criteria, a baby of defined normal birthweight (>2·5 kg) may be growth-retarded and, in the absence of any other overriding factor, its death should be categorized accordingly, although we had no such instances during the 4-year period. Ultrasound measurements of the fetus to determine gestational age in early pregnancy, and later to estimate fetal weight, make it possible to detect the small-for-dates fetus and follow its further growth velocity. Therefore, IUGR must now be regarded as a detectable condition, and most deaths from it as potentially avoidable by careful monitoring and appropriate intervention. It was for these important reasons that the new primary category of IUGR was introduced. Support for this decision, and for our choice of the 5th rather than the more generally used 10th centile to define IUGR, comes from the survey of perinatal mortality reported by the Northern Regional Health Authority Co-ordinating Group (1984), in which 35% of 'antepartum stillbirths' of normally formed singletons (and 47% when placental abruption was excluded) were of fetuses with birthweights below the 5th centile derived from local data. Where available adequate regional birthweight for gestational age date should be used.

Skilled perinatal pathology, which must include arrangements for genetic and haematological studies, bacteriological and virological investigations, and postmortem radiology, not infrequently provides the key evidence for correct classification. It provides the necessary confirmation to allocate deaths to a separate category for Infection, and to distinguish between those due to Trauma and to non-traumatic Intrapartum Asphyxia. Because deaths attributed to these causes are regarded as potentially avoidable, but by different means, they have their own separate categories in the proposed classification of TPRW. Evidence from intrapartum fetal monitoring is also helpful in showing that hypoxia occurred during labour, sometimes even in the absence of mechanical difficulty, although well before the introduction of such monitoring techniques, Bound *et al* (1956) used postmortem evidence alone to establish a separate category for these deaths.

The other new category, Unexpected Intrauterine Death, was introduced to emphasize and direct attention to the important problem of unexpected fetal deaths without perceived cause, instead of including them with other categories in the premature unknown/low birthweight and mature unknown/normal birthweight groupings. Although they accounted for only 7% of TPRW, these losses are particularly tragic since the fetuses are, by definition, normally formed and normally grown and the pregnancies have apparently been proceeding normally. A close study of these deaths, including a search for screening markers to identify women at risk in advance, might well make some of them avoidable in future. The demonstration that large transplacental haemorrhages were responsible for three of the five deaths due to Other causes suggests the possibility that feto-maternal bleeding may have also caused some of the unexplained stillbirths. This is a good example of how a classification can be used to direct attention where it is required.

There are good reasons for grouping together, in a single primary category, all deaths attributable to Hypertension, in preference to a separate category for pre-eclampsia (i.e 'toxaemia'), a viewpoint that is supported by Giersson & Patel (1983). Firstly, especially in patients who book late, it is not always possible to make the distinction between pregnancy-induced hypertension, pre-existent hypertension and the combination of pre-eclampsia superimposed on an already established hypertensive state. Indeed, because of frequent difficulty in differentiating essential from pregnancy-induced hypertension, Baird & Thomson (1969) followed an arbitrary rule to allocate to toxaemia cases which high blood pressure early in pregnancy but without other evidence of pre-existing hypertensive complications Secondly, similar mechanisms almost certainly underlie the placental dysfunction or abruption that may result in fetal death in any of these conditions, and in all of them there is the further risk of neonatal immaturity if the severity of the condition demands early delivery. Some of these deaths should probably be regarded as potentially avoidable. The use of subcategories for the losses attributed to hypertension allows comparison of trends with Baird's surveys, which had a separate main category for toxaemia and essential hypertension was listed among maternal diseases.

With rhesus immunoprophylaxis so well established, it may seem surprising that 14 pregnancies were unsuccessful because of Haemolytic Disease, but this partly reflects the hospital's function as a referral centre for this problem. Had the system of classification not been extended to include late abortions, three such losses following intrauterine death after fetal blood transfusion would have been omitted, illustrating the probability that there may be significant under-reporting of 'rhesus deaths' in some regional and national surveys of perinatal mortality.

The inclusion and classification of 94 late abortions, accounting for 30% of TPRW, reveals the extent to which very early spontaneous 'labour' and placental abruption contribute to wastage in the latter half of pregnancy. Thus, almost half of the late abortions were in the Spontaneous Preterm category, and the frequency of prolonged membrane rupture, multiple pregnancy or possible cervical incompetence as apparently predisposing factors suggests where clinical attention and research should be directed. Antepartum Haemorrhage was the next most frequent cause of late abortion and, considering only normally formed fetuses, it was also second only to immaturity following spontaneous labour as a cause of TPRW. Placental abruption was responsible for almost all these losses, including most of the late abortions attributed to antepartum haemorrhage; and the further possibility that small unconfirmed separations of the placenta may also predispose to subsequent late spontaneous abortion or premature labour is suggested by the history of second trimester bleeding in one in every four cases in the Spontaneous Preterm category.

With the continuing development and increasing use of methods for early prenatal diagnosis, it has proved useful to indicate which of the fetal abnormalities, leading to perinatal deaths or related wastage, should be regarded as having been detectable by available standard methods in time to permit selective termination of pregnancy. Except when the woman has decided against this option or when pregnancy is continued in the hope that a malformation will be amenable to surgery, each of these detectable major fetal abnormalities represents failure of a diagnostic procedure, failing to provide it when indicated, absence of any acceptable indication for it, or too late attendance or referral. In this way, the label of detectability will draw attention to the need for improved methods and skills (e.g. in ultrasonic inspection of the fetus) or for greater awareness by doctors and patients of the possibilities of specialized prenatal diagnosis. The considerable wastage caused by fetal anomalies partly reflects the referral service provided at the hospital, and also the well known high incidence of neural-tube defects in the West of Scotland, although the great majority of these had been detected by mid-pregnancy and the patient had opted for therapeutic abortion. To highlight both the contribution of fetal abnormalities to pregnancy wastage and the role of prenatal diagnosis, a separate audit of all therapeutic abortions for detected anomalies, regardless of the gestational age at termination, was considered to be appropriate.

Eventually it may become feasible to incorporate data on spontaneous abortions occurring earlier than 20 weeks gestation, but ascertainment of these may remain too difficult. In the meantime, the results of applying the proposed revised and extended classification of TPRW at one centre over 4 years are presented, not for statistical or epidemiological purposes, but as a contribution to the debate about how best to report and classify unsuccessful pregnancies, and as a model we hope others may adopt and perhaps modify.

We believe this system to be rather more informative, and less difficult, than the dual system used in the Northern Region's survey (Northern Regional Health Authority Co-ordination Group 1984), combining the obstetric classification of Baird & Thomson (1969) with the pathological classification of Bound *et al.* (1956) as used and regrouped into six main categories in the British Perinatal Mortality Survey of 1958 (Butler & Bonham 1963). It is encouraging that the Northern survey is established as a continuing process without special funding, that there has recently been established a centralized framework for a national audit in Scotland (McIlwaine *et al.* 1985), and that the Glasgow post-perinatal mortality study has also been extended nationally (Arneil *et al.* 1985). We hope our system may be tested on a regional basis, the categories used having already been adopted in a recent survey of late abortions in the Glasgow obstetric units which is now to be extended throughout Scotland.

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Does father's unemployment put the fetus at risk?

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Summary. Information concerning 15 037 singleton deliveries in 1970 showed that among the 3·5% where the male head of the household was unemployed there was no significant excess of low birthweight or preterm delivery, once social class had been taken into account. There were major differences, however, in maternal health behaviour. In order to ascertain whether the health behaviour might be a consequence of the unemployment, data were also analysed for the 658 pregnancies in women whose husbands, though employed at delivery, were subsequently unemployed. Almost identical patterns were found, implying that the association with health behaviour was not a time-related consequence of unemployment.

A study of the possible adverse effects of unemployment is particularly pertinent in an age when unemployment is a major social problem (Editorial 1984). It is assumed, not unjustifiably, that husband's unemployment may have an adverse effect on the outcome of his wife's pregnancy: the mechanisms are thought to be a combination of poverty together with the social stigma and strain associated with failure to hold down or obtain a job. In spite of such assumptions, few hard scientific data have been produced to show whether unemployment of the male head of the household is in itself an important risk factor in pregnancy (Macfarlane & Cole 1985) Such information that exists is indirect—showing that areas with high unemployment rates have high mortality rates (Brennan & Lancashire 1978) and, in particular, high rates of perinatal mortality in the larger infant (Ashford 1981). It was the purpose of the present study to quantify and qualify the direct risks involved with paternal unemployment in 1970, a time when unemployment was relatively rare (in the 1971 Census, only 3·5% of family heads were unemployed).

It is not easy to see how applicable the results are to the 1980s: on the one hand it could be argued that the unemployed in 1970 would consist predominantly of a hard core of the generally unemployable amongst whom adverse effects would be more apparent, or on the other hand that in the 1980s the unemployment problem is one which results in more stress. Data from 1970 exist, however, and it is pertinent to open the debate by publishing them.

Subjects and methods

For the British Births Survey in 1970, midwives were asked to fill in questionnaires on the pregnancy, labour, delivery and early neonatal period of all babies born in the week 5th–11th April. In the event, over 98% of births in the United Kingdom were included (Chamberlain *et al.* 1975, 1978).

Among the items collected were the usual occupation of the child's father and whether or not he was currently employed. Details of the occupation were used to derive social class codes using the classification published by the Registrar General of England and Wales (1966). Since the risk of unemployment varies with social class, comparisons of the various aspects of pregnancy and delivery between the currently unem-

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ployed and the currently employed have been carried out for this study within the social class groups. All women living apart from the father of the child have been excluded, as have all those where the father's usual occupation has either not been given or given with inadequate detail. In addition, only singleton births have been considered.

The differences which are delineated by such analyses may either be directly due to the unemployment itself or may simply be associated with characteristics of families where the father is more likely to become unemployed. To elucidate this, advantage was taken of the information available on the 80% of the surviving infants who were followed up 5 years later—at this time, the employment history of the father in the interim was ascertained From these data it was possible to identify a group of women whose husbands had been employed at the birth of the child but who had subsequently become unemployed. These women were compared with those whose husbands were employed in 1970 and throughout the next 5 years. Stratification according to social class at birth was again carried out.

Assessment of statistical significance is based on the summation of the observed and expected numbers to have both the characteristic under consideration and be unemployed; 2 × 2 tables were derived for each social class group, and then used to obtain observed and expected numbers and sampling variance (C. A. B. Smith test; Golding 1979).

Factors considered in the analysis were defined as follows:

Short mothers. Women of height <159 cm or 5 ft 2½ in as measured and recorded by the midwife.

Teenage mothers. Less than 20 completed years of age on day of delivery.

Parity. Numbers of previous pregnancies resulting in either a livebirth or a stillbirth.

New Commonwealth immigrant. Women originating from Africa, West Indies, India, Pakistan or Bangladesh.

Contraceptive use. Women delivered in April 1970 were asked whether they had used any method of contraception since January 1968.

Date of last menstrual period (LMP) uncertain. Women whose date of LMP was declared to be unknown or uncertain. In addition, those whose dates were clearly not an indication of the date of conception (for example, a previous delivery had occurred after the LMP or the size of the newborn was incompatible with the date).

Failure to have antenatal care before 28 weeks. This was identified from the dates of LMP and of the first visit for antenatal care. All instances where the LMP was uncertain have been omitted.

Failure to attend classes. These were 'antenatal classes in motherhood' (i.e. care of the baby) and 'in preparation for labour' (e.g. exercises, relaxation, etc).

History of bleeding. Any bleeding after the last period and before the onset of labour.

History of hospital admission. Hospitalization during the antenatal period (excluding admissions in labour or false labour).

Smoked throughout. Women who smoked cigarettes before, during and after the pregnancy.

Perinatal death. This included all stillbirths of gestation 28 weeks or more and all livebirths dying in the first 7 days.

Low birthweight. Because there was a certain amount of digit preference for the mostly imperial weights, the cut-off point for low birthweight was taken as 2538 g.

Gestation. This was measured in completed weeks from LMP for infants whose mother's LMP was certain.

Breast-feeding attempted. At any time during the first week of life.

Results

Husbands unemployed at the birth

Of the 15 037 pregnancies available for analysis, 523 (3·5%) were associated with paternal unemployment at the time of delivery. As expected from other national data, the proportion unemployed varied with social class, from 1·6% (41/2593) of social classes I and II, to 2·3% (204/9040) of social class III and 8·2% (278/3404) of social classes IV and V.

Ways in which other sociobiological attributes of the mothers varied are shown in Table 1, again within social class groups. The proportions of short women, teenagers and immigrants from the New Commonwealth were no different among those with unemployed husbands than would be expected from the employed group.

Table 1. Proportion of women with various sociobiological attributes according to husband's employment status and social class at delivery

Maternal socio-biological attribute	I and II		III		IV and V		Statistical significance *P*
	CU	CE	CU	CE	CU	CE	
Short (height <159 cm)	10/41 (24·4%)	664/2529 (26·3%)	84/202 (41 6%)	3185/8762 (36·4%)	132/276 (47·8%)	1376/3092 (44·5%)	NS
Teenager	3/40 (7·5%)	47/2545 (1·8%)	17/200 (8·5%)	656/8664 (7 6%)	42/273 (15 4%)	422/3058 (13·8%)	NS
Parity 0	18/41 (43·9%)	960/2554 (37·6%)	56/204 (27 5%)	3187/8840 (36·1%)	75/278 (27·0%)	1032/3121 (33·1%)	<0·01
Parity 4+	0/41 (0)	72/2554 (2·8%)	36/204 (17·6%)	568/8840 (6·4%)	62/278 (22·3%)	339/3121 (10·9%)	<0·001
New Commonwealth immigrant	4/41 (9·8%)	37/2553 (1·4%)	5/204 (2·5%)	159/8828 (1·8%)	6/278 (2·2%)	100/3124 (3·2%)	NS
Had not used contraceptives since Janurary 1968	21/41 (51·2%)	987/2540 (38 9%)	127/203 (62·6%)	4780/8805 (54·3%)	217/277 (78·3%)	2070/3114 (66·5%)	<0·001

CU, Currently unemployed; CE, currently employed; NS, not statistically significant.

Women whose husbands were unemployed were slightly less likely to be primiparae and considerably more likely to have had at least four previous pregnancies. They were less likely to have used contraceptives than women whose husbands were employed.

Comparison of the features of the pregnancies between the two employment groups (Table 2) shows that there were no significant differences in the proportion of women who attended mothercraft classes, or who had a history of bleeding or hospital admission during pregnancy. There were, however, some major differences in maternal behaviour: wives of unemployed men were consistently less likely to either know accurately the date of the LMP, to attend for antenatal care in the first two trimesters or to attend classes for preparation for labour. They were substantially more likely to smoke throughout their pregnancies.

The strongest association post-partum was shown by whether or not the mother attempted breast-feeding (Table 3). In contrast, there were no statistically significant associations with either perinatal death, low birthweight, or pre-term delivery. It should, however, be noted that numbers are too small for a moderate increase in perinatal death to reach statistical significance. There were 18 perinatal deaths amongst the unemployed group in this study, whereas 12·22 would have been expected from the social class distribution ($P = 0{\cdot}1$).

Although there was no significant excess of low birthweight among the unemployed, it is true that there was an excess among social classes IV and V (χ^2 with Yates' correction = 3·98; $P<0{\cdot}05$). We therefore carried out a further analysis on this subgroup using multiple regression and taking as the outcome (i) the probability of birthweight below 2538 g, and (ii) mean birthweight. The results showed no significant differences associated with unemployment, after controlling for maternal smoking, age and parity.

Husbands subsequently unemployed

Since the most striking differences between the unemployed and the employed groups lay in the field of maternal behaviour, we thought it important to assess whether this was the result of the unemployment itself, or an association with the characteristics of parents who were prone to unemployment. We have therefore used information collected when the surviving child was 5 years of age, and compared the group whose husbands were employed at the birth of the child but subsequently became unemployed, with those whose husbands were employed at the birth of the study child and remained employed for the whole 5 years after the study birth.

As with the group who were unemployed at the birth of the child there was a strong social class trend in the risk of subsequent unemploy-

Table 2. History of pregnancy according to husband's employment status and social class at delivery

Pregnancy characteristic	I and II		III		IV and V		Statistical significance
	CU	CE	CU	CE	CU	CE	*P*
Did not know date of LMP with certainty	10/41 (24·4%)	347/2552 (13·6%)	50/204 (24·5%)	1594/8836 (18·0%)	96/278 (34·5%)	796/3126 (25·5%)	<0 001
Failed to have ANC before 28 weeks*	4/30 (13·3%)	160/2161 (7·4%)	23/151 (15·2%)	621/7148 (8·7%)	40/174 (23·0%)	276/2311 (11·9%)	<0·001
Failed to attend preparation for labour classes	27/41 (65·9%)	1503/2535 (59·3%)	163/202 (80·7%)	6357/8784 (72·4%)	236/275 (85·8%)	2566/3106 (82·6%)	<0 01
Failed to attend mothercraft classes	22/41 (53·7%)	1588/2534 (62·7%)	151/203 (74·4%)	6281/8785 (71·5%)	222/274 (81·0%)	2446/3115 (78·5%)	NS
History of bleeding in pregnancy	7/41 (17·1%)	302/2526 (12·0%)	17/201 (8·5%)	873/8734 (10·0%)	37/272 (13·6%)	303/3092 (9·8%)	NS
History of hospital admission	7/41 (17·1%)	453/2544 (17·8%)	31/204 (15·2%)	1752/8817 (19·9%)	67/276 (24·3%)	692/3119 (22·2%)	NS
Smoked throughout pregnancy	10/40 (25·0%)	707/2545 (27·8%)	108/203 (53·2%)	3597/8813 (40·8%)	178/277 (64·3%)	1467/3115 (47·1%)	<0·001

CU, Currently unemployed; CE, currently employed, NS, not statistically significant
* Cases of known LMP only.

ment—from 1·9% (36/1877) of social classes I and II, to 6·0% (389/6524) of social class III and 10·7% (233/2172) of social classes IV and V.

Comparison of results for unemployment at the birth of the child and subsequent unemployment reveals a few slight differences in the characteristics of the mothers (Table 4). Compared to their respective base groups, women whose husbands were subsequently unemployed were more likely to be short and to have been teenagers at delivery than those whose husbands were unemployed at the birth of the child. In other respects they were similar in that both groups were more likely to have been parity 4 or greater and both were significantly less likely to have used contraceptives.

From Table 5 it is apparent that, allowing for social class, the characteristics of pregnancy were very similar for those whose husbands were unemployed at the time of delivery and those who were unemployed later. Both groups show a lack of complications of pregnancy such as bleeding or hospital admission, but exhibit similar significant associations with what is usually considered to be adverse health behaviour. Interestingly, not only are almost all the significance levels of a similar order, but the relative risks (observed divided by expected) are also very close to one another.

Table 6, demonstrates that there is a slight excess of low birthweight and short gestation deliveries whether the father is unemployed at the time of delivery, or subsequently The excess is not statistically significant and as we have already demonstrated, is largely due to the increase in smoking in these two groups. Finally, the groups who were unemployed subsequently were also less likely to have attempted breastfeeding but the difference was not statistically significant.

Discussion

It is well documented that the unemployed are disadvantaged even when compared with other recipients of State benefits such as widows, or the sick and disabled. Not only are they excluded from long-term supplementary allowances, they are less likely to receive additional State allowances and exceptional-needs grants (Townsend 1979). Even some families drawing the earnings-related supplement have incomes below the poverty line (Field 1975).

Perinatal mortality rates have been shown to

Table 3. Outcome of pregnancy and initial feeding in infants according to father's employment status and social class at delivery

	I and II		III		IV and V		Statistical significance
Outcome	CU	CE	CU	CE	CU	CE	*P*
Perinatal death	1/41 (2·4%)	33/2552 (1·3%)	6/204 (2·9%)	175/8836 (2·0%)	11/278 (4·0%)	82/3126 (2·6%)	NS
Birthweight <2538 g	3/41 (7·3%)	136/2551 (5·3%)	14/204 (6·9%)	598/8830 (6·8%)	38/278 (13·7%)	304/3127 (9·7%)	NS
Gestation <37 weeks*	2/31 (6·5%)	77/2205 (3·5%)	8/154 (5·2%)	361/7242 (5·0%)	15/182 (8·2%)	147/2330 (6·3%)	NS
Breast-feeding attempted	23/41 (56·1%)	1347/2530 (53·2%)	67/201 (33·3%)	3226/8724 (37·0%)	60/274 (21·9%)	951/3095 (30·7%)	<0·01

CU, Currently unemployed, CE, currently employed; NS, not statistically significant
* Infants with certain gestation only

Table 4. Observed and expected numbers of women having various sociobiological attributes and husbands unemployed either at time of delivery or subsequently

Maternal attribute at delivery	Currently unemployed			Subsequently unemployed		
	obs	exp†	obs/exp	obs	exp†	obs/exp
Short (<159 cm)	226	208·0	1·09	273	244·8	1·12*
Teenager	62	54·0	1·15	100	57·3	1·75***
Parity 0	149	179·1	0·83**	222	199·1	1·12
Parity 4+	98	47·6	2·06***	70	47·8	1·46**
New Commonwealth immigrant	15	13·0	1·15	10	10·8	0·93
Had not used contraceptives since January 1968	365	313·4	1·16***	407	362·9	1·12***

Significance of difference: * $P<0·05$; ** $F<0·01$; *** $P<0·001$
†Expected calculated allowing for social class

vary dramatically with social class ever since statistics have been collected (Golding & Butler 1984). Whether the association is due to increasing poverty, poor diet, inappropriate actions or stress is still a moot point. In general though, it is assumed that if the husband is unemployed the risk to the fetus will increase. It was the aim of the present study to test this assumption using data collected in the British Births 1970 Survey.

The data have shown that the main differences between pregnancies in women whose husbands were unemployed lay in maternal health behaviour. By comparing these women with those whose husbands were subsequently unemployed we have been able to show a common behaviour pattern. This suggests that maternal health behaviour and attitudes may, in some respects, be related to the husband's ability or determination to hold down a job.

It must be emphasized that since the analysis took into account social class based on the husband's last occupation, we were unable to include the important group who had never been employed. This section of the population were predominantly young teenage parents with many concomitant problems associated with youth. Nevertheless, it is unlikely that their inclusion would substantially alter the results presented here.

Our inability to show any statistically significant immediate association between paternal unemployment and perinatal mortality or low birthweight is not contradicted by secular trends. Data published by the Office of Population Censuses and Surveys have shown a decreasing perinatal mortality rate and a steady low birthweight rate throughout the period when unemployment was increasing. This is the good news. Neither this study or the national statistics, however, are able to ascertain whether

Table 5. Observed and expected numbers of women with given pregnancy characteristics and husbands unemployed either at time of delivery or subsequently

	Currently unemployed			Subsequently unemployed		
Pregnancy characteristic	obs	exp†	obs/exp	obs	exp†	obs/exp
Did not know date of LMP with certainty	156	115·6	1·35***	151	95·9	1·57***
Failed to book before 28 weeks	67	37·7	1·78***	72	41·3	1·74***
Failed to attend preparation for labour classes	426	398·8	1·07**	544	481·0	1·13***
Failed to attend mothercraft classes	395	386·6	1·02	511	479·0	1·07**
History of bleeding in pregnancy	61	52·5	1·16	49	60·7	0·81
History of hospital admission	105	109·3	0·96	127	130·1	0·98
Smoked throughout pregnancy	296	228·9	1·29***	357	271·4	1·32***

** $P<0{\cdot}01$ *** $P<0{\cdot}001$.

†Expected calculated allowing for social class.

Table 6. Observed and expected numbers of fathers unemployed, either at delivery or subsequently, having infants with various outcomes

	Currently unemployed			Subsequently unemployed		
Outcome	obs	exp†	obs/exp	obs	exp†	obs/exp
Birthweight <2538 g	55	43·9	1·25	46	39·7	1·16
Gestation <37 weeks	25	20·5	1·22	22	18·6	1·18
Breast-feeding attempted	150	178·2	0·84**	222	241·6	0·92

** $P<0{\cdot}01$.

†Expected calculated allowing for social class

there are any adverse effects occurring long after the unemployment episode.

The disturbing feature of this study lies in the fact that families who were unemployed were more likely to exhibit behaviour that would only exacerbate their problems. The most important of these must be maternal smoking. Not only is smoking dangerous for the unborn child, the habit can only increase the financial problems of the family, with consequences that include poor diet and increased tension. Whether initial smoking then results in increased stress or initial stress results in increased smoking, the result may be an ascending spiral of distress. In such circumstances it is perhaps surprising that there appeared to be so little obvious adverse effect on the fetus. Proposed analyses of the data collected on the surviving children, however, should reveal whether there are more subtle adverse long-term associations.

Acknowledgments

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Outcome of neonatal intensive care: obstetric implications for a regional service

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Summary. Data from 634 newborn babies with birthweights ⩽2000 g admitted to the South West Thames Regional Neonatal Unit in St George's Hospital since its opening in 1980 were analysed. Only 271 (43%) of the pregnancies were booked there; 200 (32%) of the babies were transferred *in utero* and 162 (26%) after delivery. Weight-specific neonatal survival rates, calculated after exclusion of lethal abnormalities showed that between 1001 and 1500 g, 79 (96%) of the 82 babies transferred *in utero* survived in 1981–1984, compared with only 57 (79%) of the 72 postnatal transfers ($P<0.02$). Under 1000 g, no such differences were found, possibly because paediatricians transferred only the fitter babies in this weight range. The birth of very-low-birthweight babies of short gestation in units unable to provide immediate resuscitation, adequate stabilization and full neonatal intensive care is a major risk factor for increased neonatal mortality. These findings support the role of regional perinatal centres as service units for antenatal transfer and neonatal intensive care, and as teaching centres.

The development of regional perinatal centres for the care of high-risk fetuses and newborn infants in the last decade has increased the numbers of babies transferred between units and has also created a demand for neonatal intensive care which has yet to be fulfilled. The Short Report (House of Commons, Social Services Committee 1980) recommended an increase in the number of intensive-care cots from the then 176 to a minimum of 400 across the country. Yet, according to the Emergency Bed Service: London Paediatric/Perinatal Group Trial Report 1983, on 17 days in 1983, no such cots were available in any of the four Thames Health Regions. In the South West Thames region, no cots were available on 251 days (81%). This is a matter of considerable concern, for Sims *et al.* (1982) reported that the survival of babies needing intensive care, but who were not admitted to their regional unit, was 30% compared with a 66% survival rate in similar babies for whom a cot was available. We know of at least 33 babies of gestation between 24 and 40 weeks (median 30 weeks) from the South West Thames region for whom postnatal transfer for intensive care was requested in 1983 but who could not be accepted at St George's Hospital. Twenty-eight were transferred to centres in each of the three other Thames regions. Ten of these babies died, and two of the five who were not transferred also died.

If resources are limited, the existing ones should be used appropriately, but with neonatal care advancing rapidly, many doctors are unaware of the potential of very-low-birthweight babies to survive Goldenberg *et al.* (1982) recently reported from Alabama that referring

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obstetricians tended to be unaware of high survival rates in very preterm babies, and so overestimated gestational ages at which 50% and 90% of preterm babies survived in a regional centre. He inferred that these erroneous beliefs might adversely influence decisions to refer to a regional centre. Under-referral of viable babies, both before and after birth, would result in increased perinatal loss. It could also be argued that over-referral of obviously non-viable babies might block cots needed for those who were larger and more viable.

Thus, within any given region, it is important for the regional centre to be aware not only of its own capabilities. but also to disseminate that knowledge. The referral of babies of very-low-birthweight or of reduced gestation can then be viewed against a background of fact. One possible use of such analysis could be to develop regional guidelines for the transfer of sick preterm babies.

Subjects and methods

To understand better the outcome of such transfers, and to assess the influence of these early factors on outcome within the South-West Thames region, data from St George's Hospital from January 1980 to December 1984 inclusive have been analysed with respect to birthweight, gestational age and place of birth. A total of 659 babies weighing $\leqslant$2000 g was admitted to the unit in that period; 25 of them (9$\leqslant$1000 g) had lethal congenital abnormalities and have been excluded from the study. The neonatal (28 day) mortality figures were calculated after the exclusion of these babies, and the data presented refer to the remaining 634 normal babies $\leqslant$2000 g who were admitted to the unit. Only 271 (43%) were booked at St George's Hospital. Of the 156 babies $\leqslant$1000 g, only 63 (40%) were so booked.

In this study, gestational age has been based upon maternal dates, supported when possible by an ultrasound examination or if dates were inadequate by ultrasound examination alone. Only when neither of these was available, was a paediatric assessment used. This was so in only one baby $\leqslant$1000 g.

The St George's Hospital neonatal unit opened in February 1980 and results from that year were worse than subsequent years. The figures and obstetric tables show data from all 5 years, but the tabulated neonatal analyses exclude 1980.

Statistical analysis of differences was by the χ^2 and Fisher's exact probability tests as appropriate.

Results

Birthweight

Figure 1 shows survival rates for babies grouped by birthweight. Neonatal survival of babies between 1501 g and 2000 g has been 100% for the last 3 years and between 1001 g and 1500 g it has been above 90% for the last 2 years. All groups show an improvement on 1980, but the most marked improvements have been below 1000 g, especially the 751–1000 g group. Survival of babies $\leqslant$750 g rose to above 80% in 1984 after running at 30–40% for the previous 3 years. In the years 1981–1983, eight (50%) out of 16 babies between 600 g and 750 g survived, the smallest being 610 g, whereas all seven babies $\leqslant$600 g died. In 1984, however, seven (87·5%) of the eight babies between 600 g and 750 g survived the neonatal period, and three of four babies $\leqslant$600 g survived, the smallest being 530 g.

Gestational age

Figure 2 shows the survival rates for babies grouped by gestational age. The improvement after 1980 is again apparent, with slower improvements since then. The major changes have occurred at <28 weeks. There have been so far a total of 16 neonatal survivors at $\leqslant$25 weeks, three of whom died in the first half of infancy. The most preterm infants to survive were three of 24 weeks born in 1983 and 1984.

Combination of data

If the data for mortality by birthweight $\leqslant$1000 g and gestational age for the years 1981–1984 are combined, Table 1 shows that survival for babies who are both $\leqslant$750 g and $\leqslant$25 weeks is significantly worse ($P<0·025$) than for the other groups combined. A baby with only one of these factors does not appear to be at greater risk, but numbers are small.

The place of birth

Table 2 shows the neonatal survival rates by birthweight groups for babies $\leqslant$2000 g who were transferred to St George's Hospital in 1981–

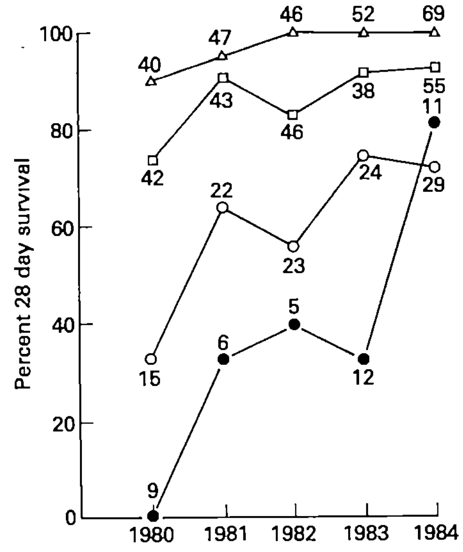

Fig. 1. Neonatal survival by birthweight (1980–1984) South West Thames Regional Neonatal Unit in St George's Hospital. (△—△) 1501–2000 g; (□—□) 1001–1500 g; (○—○) 751–1000 g; (●—●) ≤750 g.

1984. Although the overall rate was marginally better for those transferred *in utero* the difference was not significant. This overall figure hides marked variations between the different birthweight groups in the ratio of the survival rates for babies transferred *in utero* and those transferred postnatally. Under 1000 g, there were no significant differences between the two groups. Between 1001 g and 1500 g, the survival for babies transferred after birth was significantly worse ($P<0{\cdot}02$), but above 1500 g the difference was again insignificant.

Obstetric problems

Six major obstetric problems (spontaneous preterm labour; pre-eclampsia; antepartum haemorrhage, including placental abruption; prolonged rupture of the membranes; intrauterine growth retardation; abnormal cardiotocograph before labour) which preceded the births were recognized and analysed. Although many of the 595 mothers, 39 of whom gave birth to liveborn twins, had several problems, the analysis considered only the single factor deemed most important before delivery. Table 3 shows the distribution of these problems for babies booked at St George's, those transferred *in utero* and those transferred postnatally. There were no significant differences in the proportions of the problems between these three groups, even when analysed in birthweight groups of (a) ≤1000 g, (b) 1001–1500 g and (c) 1501–2000 g. Eleven babies were included who could not readily be grouped as above. Three were born normally after 37 completed weeks but with birthweights below 2 kg, four babies transferred after birth had insufficient data; four were born after labours that were induced: for rhesus isoimmunization in two, for maternal breast carcinoma in another and for hypertension and diabetes in one elderly primigravida.

Postneonatal survival

It is no longer sufficient to offer neonatal survival data as a justification for pursuing neonatal intensive care. Postneonatal mortality must also be considered. Table 4 shows the incidence of postneonatal deaths among the same four groups of babies ≤1000 g and lists the causes. Three of the eight survivors who were both ≤750 g and ≤25 weeks died, and overall six (35·3%) of the 17 survivors ≤750 g succumbed, but there was also a 12% late mortality rate in the babies born >25 weeks and between 751 and 1000 g.

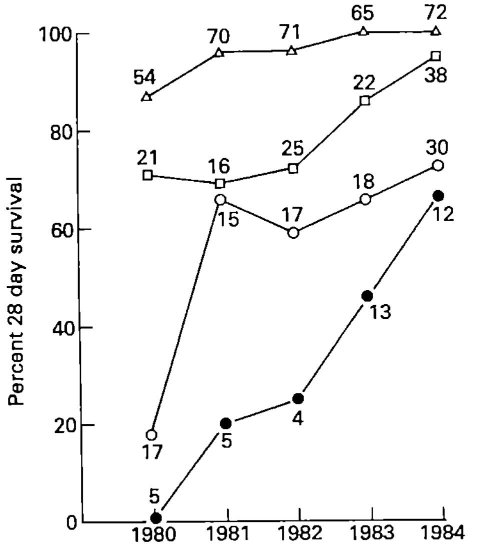

Fig. 2. Neonatal survival by gestational age (1980–1984) South West Thames Regional Neonatal Unit in St George's Hospital. (△—△) 30–35 weeks; (□—□) 28–29 weeks; (○—○) 26–27 weeks; (●—●) ≤25 weeks

Table 1. Neonatal survival of 131 infants ⩽1000 g on St George's Hospital neonatal unit, 1981–1984

Gestation (weeks)	Birthweight (g)	
	751–1000	⩽750
>25	57/84 (68%)	9/13 (69%)
⩽25	8/13 (62%)	8/21* (38%)

*$P<0·025$ *vs* other groups combined ($\chi^2 = 5·64$)

Discussion

Chiswick (1982) has suggested that 'studies that have pointed to better survival rates of babies transferred antenatally than of those transferred after birth are . . . of little value—because babies selected for neonatal transfer are generally more ill'. Our data do not show a significantly different overall survival rate for postnatal transfers. Part of the reason for this may be the high neonatal survival rate of those babies ⩽1000 g who were transferred postnatally. It may be that, in this weight range and especially below 750 g, paediatricians referred only the less ill babies (whom they considered to have a chance of survival), whereas between 1001 and 1500 g it was indeed the illest babies who were transferred, and in this study, it was only this latter group that had a significantly poorer outcome for postnatal transfers. Statements about better outcome for babies transferred *in utero* should include weight-specific data.

Analysis of the obstetric data showed that this difference in mortality could not be attributed to a difference in the frequency of the complications of pregnancy between the women delivered within and outside St George's. Thus the only difference in treatment between babies born within and outside St George's Hospital was in the delivery, resuscitation and early stabilization, for once on the St George's unit the babies were treated in an identical fashion. This implies that the critical time for these very-low-birthweight babies is during the immediate peripartum period.

An American study showed that those district hospitals regularly visited by staff from the regional perinatal centre in an outreach teaching programme monitored their sick preterm infants more frequently before the arrival of the regional neonatal transport team than those hospitals not participating in the programme (Lazzara *et al.* 1982). Babies <1700 g from the units involved in such outreach programmes were better stabilized and had fewer subependymal and intra-ventricular haemorrhages. Levene *et al.* (1982) also reported being outborn as a risk factor for intraventricular haemorrhage. There therefore seem to be good grounds for developing and expanding the present contacts that exist between district hospitals and regional units within the South-West Thames and in other regions in the UK. Such programmes should be aimed at training staff in neonatal resuscitation and early stabilization of temperature, pulse, blood pressure, perfusion, blood gases and plasma biochemistry.

This communication has concentrated on the outcome of babies with a birthweight ⩽1000 g. Self-audit within district hospitals is important to establish the birthweight and gestation at which the district hospital achieves neonatal mortality and morbidity rates comparable to those in a regional centre. It would then be possible to

Table 2. Neonatal survival by place of birth and birthweight for 363 babies ⩽2000 g transferred to St George's Hospital, 1981–1984

Birthweight (g)	Postnatal transfers (P)		Antenatal transfers (A)		Ratio of survival (P/A)
	n	% survival	*n*	% survival	
⩽750	11	81·8	12	50·0	1·64 : 1
751–1000	30	66·7	39	66·7	1·00 : 1
1001–1500	72	79·2	82	96·3	0·82 : 1*
1501–2000	50	96·0	67	100·0	0·96 : 1
All	163	82·2	200	89·0	0·92 : 1

*$\chi^2 = 5·5$, $P<0·02$.

Table 3. Summary of obstetric problems by place of birth and type of transfer 1980–1984

	Booked	In-utero transfer	Post-natal transfer
≤ 1000 g (n = 157)			
Preterm labour	23	25	35
Pre-eclampsia	12	11	6
Antepartum haemorrhage	10	8	7
Prolonged rupture of membranes	4	8	3
Abnormal cardiotocograph	2	2	0
Others	0	0	1
Totals	51	54	52
1001 g–1500 g (n = 181)			
Preterm labour	27	26	35
Pre-eclampsia	12	9	6
Antepartum haemorrhage	15	12	7
Prolonged rupture of membranes	11	9	1
Abnormal cardiotocograph	1	1	1
Intrauterine growth retardation	5	0	0
Other	1	1	1
Totals	72	58	51
1501 g–2000 g (n = 257)			
Preterm labour	57	21	25
Pre-eclampsia	26	11	10
Antepartum haemorrhage	14	12	7
Prolonged rupture of membranes	25	17	7
Abnormal cardiotocograph	1	0	0
Intrauterine growth retardation	13	2	2
Others	4	1	2
Totals	140	64	53

<1000 g: $\chi^2 = 12{\cdot}6$, d.f. = 10, $P > 0{\cdot}1$.
1001 g–1500 g: $\chi^2 = 21{\cdot}0$, d.f. = 12, $P > 0{\cdot}05$
1501 g–2000 g: $\chi^2 = 11{\cdot}9$, d.f. = 12, $P > 0{\cdot}1$

have guidelines about the advisability of transferring high-risk mothers or their very small babies.

There are two possible approaches to the deficiencies in early stabilization and resuscitation. One is to increase staffing and facilities at a district level. The other is to encourage antenatal transfer.

Wood *et al.* (1984) have recently argued that 'better provision and training of district staff in immediate care at birth would probably be of more benefit in Wessex than the setting up of a regional neonatal unit specialising in advanced neonatal intensive care.' These authors beg the question of who is to train the staff. It is appropriate that the needs of each region be met individually, but we would argue that in general the place where district staff might encounter sufficient numbers of small babies would be at a regional centre. Furthermore outreach programmes from a regional centre are one way in which standards of training can be maintained and improved. It has been the theme of this paper that early resuscitation and stabilization of sick preterm (and term) babies is of crucial importance to neonatal outcome. There is evidence that doctors' expectations may be too low when considering the potential of very-low-birthweight babies (Goldenberg *et al.* 1982). Regional centres should modify this opinion to achieve more appropriate expectations and care for such babies. Thus, if the approach to improving current practices in resuscitation and early stabilization at district hospitals is to be by

Table 4. Late deaths in neonatal survivors ≤1000 g (1981–1984)

Gestation (weeks)	Birthweight (g)		Causes
	751–1000	≤750	
>25	7/57	3/9	5 Bronchopulmonary dysplasia 4 Sudden infant death syndrome 1 Necrotizing enterocolitis 1 Intussusception 1 Sub-acute bacterial endocarditis 1 Septicaemia
≤25	0/8	3/8	

increasing staff and resources at that level, the regional perinatal centre still retains a vital role in training and education. Indeed, it is hard to see how else the stated aims of Wood *et al.* (1984) can be achieved.

There is evidence to support antenatal transfer to a regional perinatal centre as a manoeuvre to improve neonatal survival (Lobb *et al.* 1983; Blake *et al.* 1979). However, increasing numbers of antenatal transfers present at least two problems. First, they impose a considerable workload on the obstetricians and midwives in the regional perinatal unit. They may also cause problems of bed occupancy on the antenatal wards, particularly if some women are reluctant to return to the referring unit once the threat of preterm labour has receded. Secondly, a neonatal intensive care cot must be held open for the baby of a transferred woman who may give birth within a day or so. In 1980–1981 at St George's Hospital, the mean delay between antenatal transfer and delivery was 8·6 days (McIntosh & Bone 1984). Whilst intensive care cots are not necessarily held open for the babies throughout this antenatal stay, the cots are nevertheless blocked for at least part of that time, and requests for postnatal transfer may have to be declined.

Thus, if there is to be a trend towards antenatal transfer, which is already occurring in the South West Thames region, there must be a concomitant provision of extra neonatal intensive care cots in the regional unit. The present provision of such cots is inadequate in the four Thames regions. Within the South West Thames region, the situation is such that already the regional unit had to decline requests for postnatal transfers on 80% of days according to the Emergency Bed Service: London Paediatric/Perinatal group Trial Report 1983. With increasing numbers of antenatal transfers this unacceptable situation will deteriorate until more cots become available.

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Analysis of impedance cardiography longitudinally applied in pregnancy

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Summary. Data gathered during a longitudinal study of cardiac output throughout pregnancy, measured by application of impedance cardiography, have been reassessed in respect to individual items of measurement. Examination of the pattern of change in these values did not reveal any flaw in the proposition that impedance cardiography, with the invocation of the Kubicek equation, can confidently be applied in such a study.

Some years ago (Atkins *et al.* 1981*a*) we presented the results of a study of changes in cardiovascular dynamics relating to the period before, during and after pregnancy. Our observations led to results which in some particulars ran counter to established teaching. Most notable was the finding that stroke volume and cardiac output, having increased from their pre-pregnancy levels to reach a maximum value at about 12 weeks gestation, remained at approximately those levels for a further 8 weeks and thereafter gradually fell, so that by term they were below their pre-pregnancy values, which were regained only 3–6 months postpartum. The patterns of change were the same irrespective of the position of the woman at each study period (Atkins *et al.* 1981*b*).

The techniques used in that study included the application of impedance cardiography, according to the method introduced by Kubicek *et al.* (1974). This method of assessing stroke volume and cardiac output has been found to provide results comparable to those attained by application of other established techniques in a variety of situations (Muzi *et al.* 1985), including that of pregnancy (Secker *et al.* 1979; Milsom *et al.* 1983*a*). However, scepticism has been expressed (Milsom *et al.* 1983*b*) about the use of this method in longitudinal studies in pregnancy, because of the possibility that some of the physiological changes characteristic of pregnancy influence the output of the cardiograph in a so far unidentified manner.

It seems unlikely that the anatomical changes in the contour of the thoracic cage relating to pregnancy could lead to such a distortion. A significant increase in stroke volume and cardiac output was identified during the first 12 weeks gestation, before such anatomical changes become marked, and the contrast between pre-pregnancy and postpartum values was sustained for several weeks after delivery. If there is indeed a fallacy inherent in the attempt to apply a simple analysis of impedance cardiography to a longitudinal study in pregnancy, it is likely to be elsewhere. In an attempt to identify such a fallacy we have re-examined our accumulation of the component measurements from which the values of stroke volume (and hence of cardiac output) were derived.

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Subjects and methods

The value of stroke volume (SV) was derived from the Kubicek equation:

$$SV = \rho\left(\frac{L}{Z_0}\right)^2 T\,(dZ/dt)_{min}$$

where ρ is the resistivity of the blood; L is the distance between the inner two Mylar strip electrodes applied to the subject; Z_0 is the mean impedance between these two electrodes; T is the ventricular ejection time; and $(dZ/dt)_{min}$ is the minimum value of the first time derivative of ΔZ (which is the impedance change throughout the cardiac cycle).

The value of the resistivity of blood was derived from knowledge of the haematocrit (assessed at each study session) by application of the established equation (Mohopatra & Hill 1975). The pattern of change in haematocrit recorded by us (Atkins *et al.* 1981*a*) conformed to that which is generally accepted and needs no further comment.

There were 29 subjects in the original study. However, two of these pregnancies ended in spontaneous abortion and the basic data relating to two others have been mislaid. Thus this communication relates to 25 subjects, each of whom had a normal pregnancy although, two patients developed mild gestational hypertension late in the final trimester.

The individual values of L, T, Z_0 and dZ/dt obtained from these 25 subjects, whilst they were in the left tilt position, at intervals from 8 weeks gestation to 6 weeks postpartum were examined and the mean values relating to each time period assessed.

Results

Graphs of the mean values are shown in Figs 1 to 4. As a brief indicator of the variability of the longitudinal changes typically observed, Table 1 shows the mean and SD of the differences between each subject's 8 week and 36 week values. The same statistics are also given for the differences between the 8 weeks pregnant and the 6 weeks postnatal values, together with the

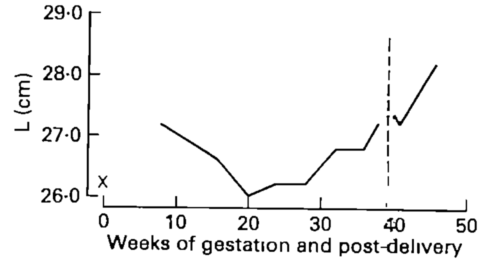

Fig. 1. Mean values of the distance between the inner electrodes as measured in 25 subjects, lying in the left tilt position, at various times during pregnancy and postpartum.

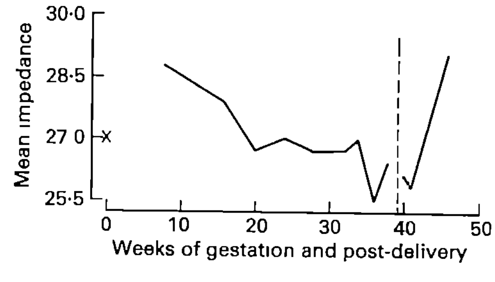

Fig. 2. Mean values of the mean impedances as determined in the subjects referred to in Fig. 1

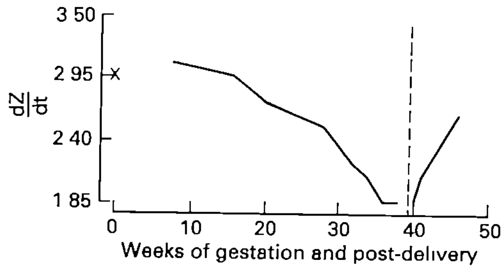

Fig. 3. Mean values of the derivative dZ/dt as determined in the subjects referred to in Fig 1

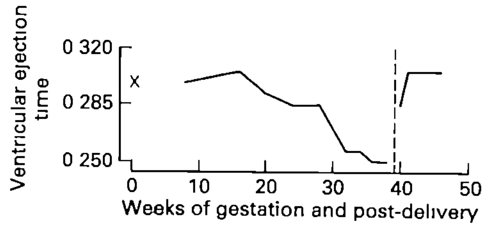

Fig. 4. Mean values of ventricular ejection time as determined in the subjects referred to in Fig 1

Table 1. Means and standard deviation of values d_1 and d_2, with the number of available observations and the level of statistical significance, where relevant, at which the mean change is different from zero

	L CV_8 7·5%		Z_0 CV_8 10·3%		dZ/dt CV_8 21·6%		VET CV_8 5·3%	
	d_1	d_2	d_1	d_2	d_1	d_2	d_1	d_2
Mean	0·58	−1·14	3·71	−0·02	1·21	0·40	0·049	−0·005
SD	2·24	2·18	2·59	3·28	0·57	0·46	0·028	0·024
n	20	23	20	23	20	23	20	23
	—	$P<0·02$	$P<0·001$	—	$P<0·001$	$P<0·001$	$P<0·001$	—

CV_8, Percentage coefficient of variation of the 8 week value; d_1, difference between the 8 week value and the 36 week value; d_2, difference between the 8 week value and the 6 week postpartum value; VET, ventricular ejection time

statistical significance of the observed mean difference as assessed by *t*-tests.

As measures of the subject to subject variation the percentage coefficient of variation (100 × SD/mean) is also quoted for the 8 week value of each variable.

Generally it can be seen that most of the component variables showed statistically significant changes from 8 to 36 weeks as did their derivatives—stroke volume and cardiac output.

(i) *L (Fig. 1).* The mean value of the distance between the inner electrodes (which was itself the mean of the distance as measured at the front and the back of the subject) fell by just over 1 cm from 8 weeks to 20 weeks, then rose steadily but by a small amount throughout the remainder of pregnancy. The mean value at 38 weeks was 0·8% higher than that at 8 weeks.

(ii) *Z_o (Fig. 2).* The mean value of the mean impedances at 38 weeks was 8·4% lower than that derived from measurements made at 8 weeks.

(iii) *dZ/dt (Fig 3).* The mean value of this derivative at 38 weeks was 36·5% lower than that obtained at 8 weeks.

(iv) *T (Fig. 4).* The mean value of the ventricular ejection time at 38 weeks represented a reduction by 19·0% from that assessed at 8 weeks.

Discussion

In our search for changes in body structure which might have negated the value of a simplistic interpretation of impedance cardiography as a method of measuring the progressive changes in stroke volume and cardiac output throughout pregnancy, we are of the opinion, for reasons stated earlier, that simple changes in the anatomical configuration of the thorax is not such a factor, and that changes in, for example, pulmonary perfusion, cardiac orientation or the level of the diaphragm would be required, these being beyond interpretation by the Kubicek equation. The progressive changes in haematocrit were assessed at each study session and incorporated in the equation.

We cannot explain the observed pattern of change in L; possibly it reflects changes in the relaxed position which pregnant women find to be most comfortable. In any case, the variations of the value of L were much too small to account for a significant part of the observed changes in stroke volume, the mean value of which in our series had, by 38 weeks, fallen by 38·7% from the mean value at 8 weeks.

Burg *et al.* (1974) investigated pregnancy-related changes in left ventricular ejection time (LVET) by measuring systolic time intervals. They reported that at an undefined time in the final trimester LVET was 6 9% lower than it had been at some undefined time in the first trimester, and 8·3% lower than the pre-pregnancy value. Although the reduction is smaller than is that of T from 8 to 38 weeks in our series, the direction of change is the same. Ueland *et al* (1969) and Rubler *et al.* (1977) observed a similar trend, which was not statistically significant, in subjects studied in the left lateral position. However, Katz *et al.* (1978), who like Rubler *et al.* (1977) used a non-invasive technique, did not derive confirmatory results from their study.

Finally we have to consider the possibility that pregnancy-associated changes in the tissue fluid and electrolyte content, concentration and distribution influence the output of the cardiograph. The results of the analyses presented here reveal that there is a change in the mean impedance (Z_0), albeit a rather small one, which might reflect alterations in the constituents of the chest wall. However, the direction of change between the eighth and 38th week (a fall in Z_0) is such that had an assumption been made that there was no change, and the value found at 8 weeks been applied in the Kubicek equation from which the stroke volume at 38 weeks was derived, the reduction in stroke volume so calculated would have appeared to have been even greater than we reported.

In summary, we have been able to discover no evidence to suggest that the application of the Kubicek interpretation of impedance cardiography in the measurement of progressive changes in stroke volume throughout pregnancy is intrinsically flawed. We re-iterate our hope (Atkins *et al* 1981*a*) that other investigators, applying an alternative non-invasive technique of measurement, will help to establish whether or not our original conclusions are correct

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The measurement of cardiac output by electrical impedance plethysmography in pregnancy. Are the assumptions valid?

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Summary. The assumptions of the Kubicek technique for measurement of cardiac output by detection of changes in the chest wall electrical impedance have been re-examined. The fall in cardiac output in the latter half of pregnancy which Crawford's group calculated using the Kubicek technique can be almost entirely accounted for by a fall in the term dZ/dT of the Kubicek equation, as pregnancy progress. One key assumption of the Kubicek technique is a constant ejection flow rate equal to the initial flow as the pulmonary valve opens, which is multiplied by the estimated ejection time to obtain stroke volume. Initial flow rate is represented by the term dZ/dT in the Kubicek equation. Although this assumption has been shown to give a reasonable correlation with other techniques for measurement of cardiac output in the non-pregnant state, this may not be so for longitudinal studies in pregnancy because of the changes in lung mechanics and in the circulation which occur in this state. Crawford's data emphasizes the necessity for validating the Kubicek technique very critically during pregnancy.

Non-invasive measurements of cardiac output are badly needed and in particular for pregnancy. Dr Selwyn Crawford and his colleagues have studied the electrical impedance plethysmography technique in pregnancy for several years and report their latest findings in this issue of the Journal (p. 717). Using this technique (Atkins *et al.* 1981) cardiac ouput appears to rise by approximately 25% reaching a plateau at 12–20 weeks of pregnancy, but then falls to non-pregnant levels by the end of pregnancy, even when measured with patients in the left lateral position. Although small, and usually statistically non-significant, falls in cardiac output at the end of pregnancy have been reported previously (Metcalfe & Ueland 1974), a fall to below non-pregnant levels at the end of pregnancy would have profound biological significance. The blood flow to the uterus alone is 500–700 ml/min (de Swiet 1980), about 15% of the cardiac output as determined by Crawford's group (Atkins *et al.* 1981). Since the a-v O_2 difference decreases in pregnancy (Bader *et al* 1955) other organs such as the kidney and gastro-intestinal tract that do extra work and therefore require extra oxygen must need an increased blood flow. If Crawford's findings (Davies *et al.* 1986) are correct, the remainder of the tissues would have to receive a blood flow reduced by perhaps 30% to allow such an increase in blood flow elsewhere in the presence of an overall decrease in cardiac output. It is

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therefore essential to examine very carefully the assumptions in the Kubicek equations relating changes in electrical resistance of the thorax to cardiac output. In particular, are these assumptions likely to be valid throughout pregnancy?

Fundamental physical principles

The Kubicek technique depends on the measurement of right ventricular output as detected by the change in electrical resistance associated with the ejection of blood into the pulmonary bed (Kubicek *et al.* 1966). Electrical resistance was measured in a vertical direction from top to bottom of the thorax (Fig. 1a). An electrical current generator (I) caused an interrogating current to enter and leave the body through the outer electrodes (E1 and E2). The resistance to the flow of this current was measured in terms of the resulting voltage (V) detected above and below the thorax by the inner pair of electrodes (E3 and E4). (This avoids errors due to variation in skin contact resistance). For most of the distance between the pairs of electrodes, the rib-cage may be considered to form a fairly rigid container (Fig. 1b) surrounding a central core of solid or fluid filled incompressible tissue, together with two columns of partially air filled tissue (cross-section Fig. 1c). The resistance to the flow of electricity through the incompressible component will be virtually constant through each cardiac cycle. Its resistance to electrical flow will be similar to, though generally greater than, that of blood.

Each lung may be considered to consist of a three dimensional network of electrically conducting sheets and filaments surrounding non-conducting air filled cavities (Fig. 1c). The electrical resistance of the lung 'sponge' will vary as non-conducting air is displaced by conducting blood injected into and flowing out of it during each cardiac cycle. While the resistance of the tissue component will hardly change during a cardiac cycle that of the blood capillary component will vary with the volume of blood contained.

If a fixed quantity of blood could be injected into the pulmonary vascular bed and prevented from escaping, an increase in electrical current should occur corresponding to the proportional increase in conductive blood in relation to the existing non-variable conductive material between the electrodes in the thoracic cavity. This forms the basis of the first section of the calculation.

Unfortunately, blood flows out of the vascular bed immediately the pressure rises and stroke volume has to be estimated by extrapolation of initial flow. This forms the second section of the calculation.

Relation between change in electrical impedance and lung blood volume

Kubicek *et al.* (1966) give the resistivity of blood (ρ) as 150 Ω.cm. This means that a 1-cm cube of

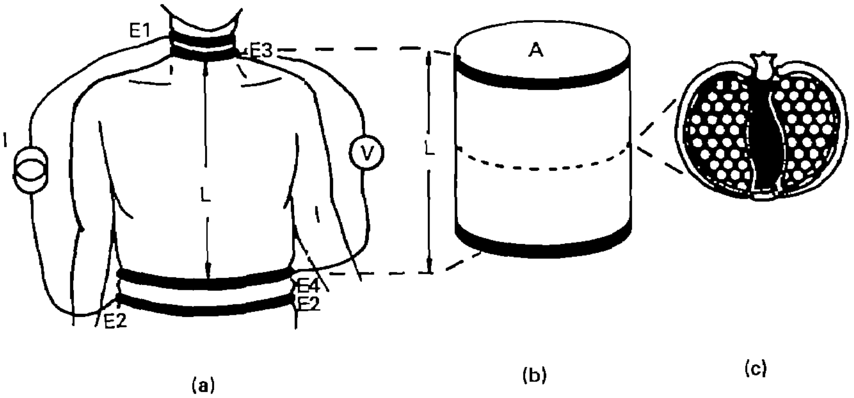

Fig. 1. (a) An interrogating current (I) between electrodes E1 and E2 causes a voltage (V) to appear between electrodes E3 and E4 which varies with the electrical impedance of the tissue between them. (b) In the model, the body tissues above and below the lungs are represented by the upper and lower ends of the cylinder cross-section A m^2 and length L m. (c) Cross-section of thorax to show highly conducting central core (heart and great vessels) and variable lower conducting periphery (air and blood filled lungs).

blood would offer a resistance of 150 Ω to flow of electricity from one face to an opposite face. If two such cubes were placed end to end, the combined resistance would be 300 Ω. On the other hand, if they were placed side by side so that two paths were available for conduction, the combined effect would be 75 Ω: i.e. resistance of a solid is proportional to path length and inversely proportional to cross-sectional area.

We will take as a model of the thorax a cylinder of length L (between the electrodes) and cross-sectional area (A) (Fig. 1b). Its height (L) is the distance between the voltage sensing electrodes, and its cross-sectional area (A) is equal to that of that of the body section at the lower voltage sensing electrode (E4). The top and bottom surfaces of the cylinder are assumed to be highly conducting representing the absence of non-conductive air above and below the lungs. Initially, consider the cylinder to be completely filled with blood. The resistance from top to bottom would then be

$$Z=\rho \times L/A \quad \ldots \text{e2·1}$$

However, it is not a uniformly filled cylinder, some is tissue, some is blood and some is air. We will assume the tissue resistance does not change during a cardiac cycle. Then, although the resistivity of the tissue component may differ from that of blood, we may consider tissue to be electrically equivalent to a fixed quantity of blood.

The resistivity of the lung 'sponge' will depend on the proportion of blood and blood equivalent in each cubic cm. Let this be n%. Then average lung resistivity is $\rho \times 100/n$ i.e. if all air were expelled (n=100), it would offer the same resistance as blood. It is more convenient to express this in terms of the mean % conductive material in the whole thoracic contents which we will call N%, and treat as if it were blood. We may now express the total resistance between inner electrodes (Kubicek's Z_0) as

$$Z_0=\frac{\rho\times L\times 100}{A\times N} \quad \ldots \text{e2·2}$$

Now total thoracic cylinder volume is L×A and N% of this is equivalent to blood, so

Thoracic equivalent blood volume=L×A×N/100

Now when extra blood is injected, N will change in the ratio of the stroke volume to total thoracic equivalent blood volume.

Let stroke volume be dV and the resulting change of thoracic resistance be dZ

$$\text{Then } dZ=Z_0\times\frac{dV}{L}\times\frac{100}{A\times N} \quad \ldots \text{e2·3}$$

$$\text{But from e2·2 } \frac{100}{A\times N}=\frac{Z_0}{\rho\times L} \quad \ldots \text{e2·4}$$

Substituting

$$dZ=Z_0\times\frac{dV\times Z_0}{L\times\rho\times L} \quad \ldots \text{e2·5}$$

or

$$dV=\rho\times\frac{L^2}{Z_0^2}\times dZ \quad \ldots \text{e2·6}$$

the well known Kubicek relation.

Thus compensation for air volume is built into the Z_0 term (mean resistance between E3 and E4) and so variation of functional residual capacity with shape, position, etc., should not affect the result in so far as contained air is concerned. Kubicek does specify, however, that measurements were made while the subjects held their breath (Kubicek *et al.* 1966), and this was presumably to increase the accuracy of measurement of ejection time which is a key factor in estimating dZ.

Estimation of dZ by extrapolation of initial flow

In the above, theoretical static comparison was made before and after displacing dV of non-conducting air by conducting blood. In the real situation, since blood is leaving the lungs and entering the left atrium during systole, dZ can not be directly measured. Kubicek overcame this by assuming a constant ejection flow rate equal to the initial flow as the pulmonary valve opens and multiplying this by an estimated ejection time. Originally, he drew a tangent to the dZ-time curve at the start of ejection (Kubicek *et al.* 1966). Initially the rise of pressure in the pulmonary bed will be small and hence the increased resistance to blood flowing into the lung and flow out of the lung will not have started. He measured the height of this tangent when the pulmonary valve phono signal indicated end of systole (delta Z, T_1 in Fig. 2b and Fig. 2d). This represents the volume that would result if the initial flow rate were maintained for the full ejection time (Fig. 2c). Later, Kubicek *et al.* (1974) realized that closing time information is contained in the slope of the dZ curve, and

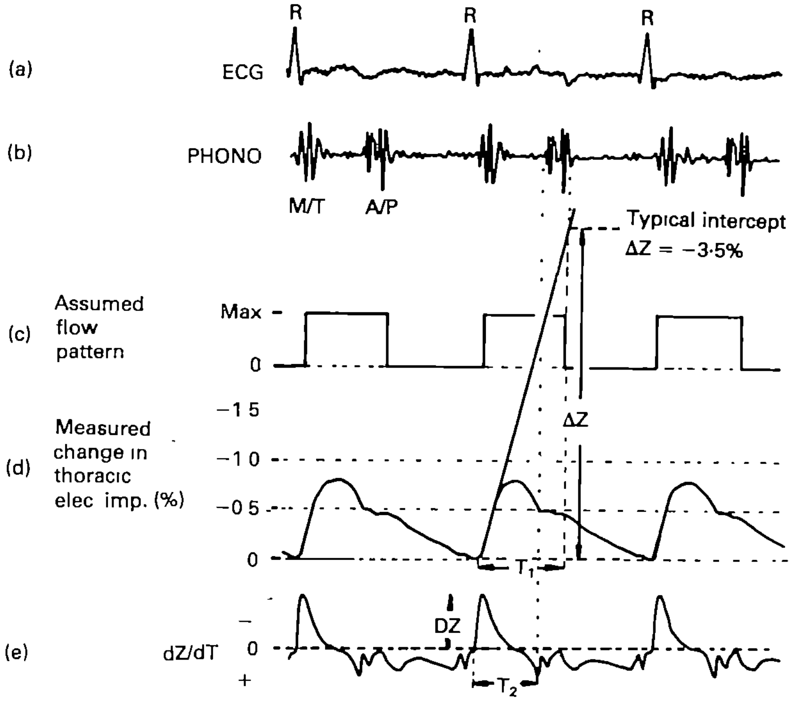

Fig. 2. Diagrammatic representation of polygraph tracing and other variables involved in the calculation of stroke volume by alterations in thoracic impedance (see text, adapted from Kubicek *et al.* 1966).

used this instead of the phono signal. A signal giving the rate of change of resistance was generated electronically and is represented by Fig. 2e. The magnitude of the upwards peak DZ, (Fig. 2e) represents the highest slope of the delta Z curve. The following downwards peak marked the time when reverse flow back into the heart is arrested by valve closure T_2. T_2 will always be shorter than T_1, since T_1 is measured to the last vibration of the last valve to shut, and T_2 to the first sign of flow arrest by the first of the pair. Stroke volume was then assessed as $DZ \times T_2$.

Discussion

Clearly the assumption of constant flow is only an approximation since the valves would not close unless flow reduced to zero at the end of systole. Flow rate at any instant during systole will depend both on the pressure difference between ventricle and vascular bed available to drive the blood and on the capacity of the vasculature to receive it. For instance, if the lung vascular bed were very elastic and of large capacity, a constant driving pressure could exist and a fairly constant flow take place. The tangent approximation might then be justified. If the bed were less elastic, the stroke volume could not be accommodated by distension and the initial flow will be reduced by the increasing pressure required to distribute the bolus. The non-linear elasticity of vascular walls (Damask 1978) will enhance this difference. Yet the initial dZ/dT will not be altered since it occurs at minimum distension. The initial displacement of air may also be increased by pulmonary compression due to transient distension of the aorta by left ventricular ejection. This component, though probably small, will add to the slope of dZ/dT in a manner that depends on the elasticity of the aortic walls. Kubicek *et al.* (1974) consider the difficulties of dZ measurement with grossly abnormal curves related to cardiac anomalies but do not appear to deal with lung vascular factors.

Any other factor, for instance the increase in total blood volume of pregnancy, which might change the hydrodynamic properties of the lung vasculature, could produce similar changes in the values of dZ registered for a given stroke volume.

Serial comparison of cardiac stroke volume by change in thoracic electrical impedance is only valid if any variation of the ejection flow-time profile during the period is known and compensated for. The term dZ/dT×T in the expression was found empirically to provide a relation between impedance change and stroke volume as assessed by independent techniques, such as dye dilution (Kubicek *et al.* 1966). If the time course of ejection of blood from the right ventricle were nearly a square wave (Fig. 2c), and if blood were not continually leaving the lungs to enter the left atrium, this function would indeed describe the change of electrical resistance due to the ejection of blood into the lungs, and therefore stroke volume, accurately. But, as discussed above, these assumptions are not true; moreover, it is likely that flow/time profile and lung drainage will vary during pregnancy, particularly in view of the 19% reduction in ventricular ejection time at 38 weeks, compared to that at 8 weeks. During pregnancy, the ribs splay outwards (Thomson & Cohen 1938) and more than compensate for the elevation of the diaphragm by the expanding uterus. The lungs are thus changing shape towards the end of pregnancy, and a change of vascular resistance and capacitance is to be expected on these grounds alone.

The peripheral resistance is reduced in pregnancy (Bader *et al.* 1955), at least in part due to the action of prostanoids such as prostacylin (Lewis *et al.* 1980; Goodman *et al.* 1982), and these agents also affect pulmonary vascular resistance (Higenbottam *et al.* 1984). Changes in pulmonary vascular resistance may also be caused by the reduction in residual lung volume (Knuttgen & Emerson 1974) in pregnancy. During general anaesthesia there is also a fall in functional residual capacity. When Milsom *et al.* (1983) compared impedance and dye dilution techniques at caesarean section, the results were similar antepartum in a series of epidural patients, but differed markedly in a general anaesthesia series. This would be consistent with a change of flow variables during systole caused by low functional residual capacity.

Changes in haematocrit will affect blood viscosity. Alterations in blood viscosity, total blood volume, pulmonary vascular resistance and heart rate, all of which occur in pregnancy, will all affect the time course of ejection of blood from the right ventricle.

These alterations, rather than a change in cardiac output, may well account for a large proportion of the change in the dZ/dT term observed by Davies *et al.* (1986). Inspection of the data indicate that it is the marked fall in the term dZ/dT which accounts for the majority of the perceived fall in cardiac output.

If the Kubicek equation is to be used to compare stroke volumes in late pregnancy, it must be shown that the term dZ/dT×T describes stroke volume sufficiently accurately in the physiological and pathological situations in which it is used. This will require supplementary measures, perhaps by ultrasonic range gated Doppler. Such measurements will be complex and difficult, but if achieved, would not only resolve this problem but open the way for use of the impedance technique to studying non-invasively fundamental changes of far reaching importance in the pulmonary circulation in pregnancy and in other conditions.

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Pregnancy in Jamaican women with homozygous sickle cell disease. Fetal and maternal outcome

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Summary. The outcome of 664 pregnancies in 297 Jamaican women with homozygous sickle cell (SS) disease over the period 1959–1984 was reviewed. Overall, the spontaneous abortion rate was 118 per 1000 pregnancies, the stillbirth rate 128 per 1000 births, and perinatal mortality 171 per 1000 births. There was a striking secular increase in both spontaneous abortions and stillbirths which was accounted for, in part, by a trend for abortions to increase with maternal age up to the age of 30 years, a greater proportion of patients in the high-risk 25–29 year age group occurring in the 1980–1984 period. Another factor contributing to the poor obstetric performance in the 1980–1984 period was probably an increased survival and pregnancy rate in high-risk patients. Seven women had pregnancy-related deaths giving a pregnancy mortality rate of 1·1%.

The effect of pregnancy on patients with sickle cell disease and the effects of maternal sickle cell disease on the outcome of pregnancy have been the subject of many communications. In a recent comprehensive review of the literature, Milner *et al.* (1980) tabulated data from 13 reports over a 24-year period with a total of 468 pregnancies in women with homozygous sickle cell (SS) disease. These authors presented the largest single series to date with details in a further 123 pregnancies.

There is also evidence of geographical variability, the poorer outcome of pregnancy in West Africa (Hendrickse *et al.* 1972) reflecting the greater prevalence of infections especially malaria, more frequent severe anaemia, and almost certainly the availability of health services. Surprisingly a geographical variability may also occur within the United States, the experience of some groups (Fort *et al.* 1971) contrasting strikingly with that of others.

From the accumulated published information, certain observations and trends emerge but their interpretation is complicated by such geographical variation, by the relatively small number of cases in most individual series, by variation in definitions and observer methods, different selection biases in the groups studied, varying degrees of therapeutic intervention, and by secular effects.

A large series of pregnancies from a single institution has the advantage of decreasing the effects of many of these different variables and allows a more comprehensive analysis of factors determining the outcome of pregnancy in women with SS disease. An analysis of 664 pregnancies occurring in Jamaican patients is therefore presented

Subjects and methods

The patients attended the Sickle Cell Clinic of the University Hospital of the West Indies,

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Kingston, Jamaica and a group of peripheral sickle cell clinics, all operated by the staff of the MRC Laboratories. The study was confined to patients with homozygous sickle cell (SS) disease born between 1 January 1940 and 31 December 1969 who had experienced at least one pregnancy. Attempts were made to include all patients known to the clinic fulfilling these criteria including those who had died, defaulted, or emigrated provided they had reached the age of 14 years when last seen. In the case of emigrated patients, only the clinical course up to the time of emigration was included. The study group included 297 women of whom 230 were still attending clinics, 25 had defaulted and were untraceable, 21 had emigrated, and 21 had died.

The hospital dockets and sickle cell clinic files of all patients were reviewed retrospectively and verification of data performed by patient interview (by GRS) in 45% of patients (59% of those still attending clinic). Abortions were defined as spontaneous termination of pregnancies before the fifth month of gestation Data recorded included date of delivery, duration of gestation, mode and site of delivery, fetal outcome and weight. The pregnancies took place between 1959–1984 and throughout this period, management was essentially conservative. Blood transfusion was used where indicated on the basis of falling haemoglobin levels and occasionally during the management of vaso-occlusive complications but no patients received exchange or regular transfusions.

Analysis of data was performed using the Statistical Package for the Social Sciences (SPSS). Trends were assessed by logistic regression using GLIM and their significance assessed by the χ^2 test. The diagnosis of SS disease was based on standard criteria including haemoglobin electrophoresis under alkaline and acid conditions, compatible HbA_2 levels, and family studies where possible.

Table 1. Overall outcome of 656 singleton pregnancies in 297 women with homozygous sickle cell disease

Spontaneous abortions	72
Terminations	25
Stillbirths	69*
Still pregnant at time of study	11
Outcome unknown	10
Live births	469
Total pregnancies	656

* Including two maternal deaths with viable children.

Results

There was a total of 664 pregnancies and 672 conceptions (eight twin pairs) in 297 women; 113 women had one pregnancy, 85 had two, 53 had three, 23 had four, 15 had five, five had six, one had seven, and two women had nine pregnancies. The age of menarche had been recorded prospectively (to within 1 month) in 114 patients, was recalled to within 6 months in 126 patients, and was unknown in 57 patients. In the former two groups in whom menarche was recorded with accuracy of at least ± 6 months, the mean interval between onset of menarche and onset of first pregnancy was 6·1 years (range 1 month–21·7 years). The age at outcome of first pregnancy was known in 294/297 (99%) of women; the mean age was 21·9 years (median 21·2 years, range 15·1–37·4 years). The mean age at delivery of first live infant was 22·0 years (median 21·3 years, range 15·1–37·4 years).

The overall outcome of the 656 singleton pregnancies is summarized in Table 1. The result was unknown in 21 (11 still pregnant at time of study, six with inadequate history, three defaulted and one emigrated while still pregnant). Termination of pregnancy, most commonly between 3 and 4 months, was performed in 25 cases, the most common indication being failure of contraception. Of the 610 remaining pregnancies with known outcome, spontaneous abortions occurred in 72 giving an abortion rate of 118·0 per 1000 pregnancies. Since pregnancies resulting in abortions are no longer at risk for stillbirths, the 69 stillbirths which occurred in a group of 538 pregnancies at risk, gave a stillbirth rate of 128·3 per 1000 pregnancies. Of the 469 live births, 31 died within 1 year, 23 in the first week and another within the first month. The neonatal deaths were therefore almost entirely (23/24) in the first week, 19/24 (79%) occurring within 3 days of birth. The perinatal mortality rate was 171·0 per 1000 total births, the infant mortality rate 66·1 per 1000 live births, and the total fetal loss (spontaneous abortions and perinatal deaths) 269·0 per 1000 pregnancies.

There was a striking increase in both abortion and stillbirth rates over the period of study, particularly in the last 5-year period (Table 2), the trends being significant at the 5% and 0·1% levels respectively. Neonatal deaths fell steeply

Table 2. Outcome of pregnancy in women with homozygous sickle cell disease (SS) according to calendar year

Year of delivery	*n*	Induced abortions	Spontaneous abortions		Stillbirths		Live births	Early neonatal deaths		Perinatal death rate**	Overall fetal wastage*
			No	(rate)*	No.	(rate)**		No.	(rate)***		
<1959	4	0	0		0		4	0		—	—
1960–1964	37	0	2	(54)	2	(57)	33	5	(152)	200	243
1965–1969	78	0	7	(90)	7	(99)	64	2	(31)	127	205
1970–1974	160	3	17	(108)	12	(86)	128	6	(47)	129	223
1975–1979	195	9	21	(113)	20	(121)	145	6	(41)	158	253
1980–1984	158	13	24	(166)	26	(215)	95	4	(42)	248	372
Total	632†	25	71		67		469	23			

† Year of delivery unknown in three pregnancies.
* Rate per 1000 pregnancies; ** rate per 1000 births; *** rate per 1000 live births

Table 3. Outcome of pregnancy in women with homozygous sickle cell disease (SS) according to maternal age

Age (years)	*n*	Induced abortions	Spontaneous abortions		Stillbirths		Live births	Early neonatal deaths		Perinatal death rate**	Overall fetal wastage
			No.	(rate)*	No	(rate)**		No	(rate)***		
15–19	130	2	12	(93)	10	(86)	106	5	(47)	129	211
20–24	275	11	26	(98)	32	(134)	206	10	(49)	176	258
25–29	172	9	31	(190)	17	(129)	115	6	(52)	174	307
30–34	43	2	2	(49)	7	(179)	32	2	(62)	231	268
35–39	8	1	0		1		6	0			
40–44	1	0	0		0		1	0			
Total	629†	25	71		67		466	23			

† Maternal age unknown in six pregnancies.
* Rate per 1000 pregnancies; ** rate per 1000 births, *** rate per 1000 live births

after the 1960–1964-year period but showed no consistent secular trend thereafter. The outcome of pregnancy according to maternal age (Table 3) indicated a significant increase ($P<0{\cdot}05$) in spontaneous abortions with maternal age up to the age of 30 years although a less obvious trend in stillbirths. There was a greater proportion of the high-risk age group (25–29 years) in the 1980–1984 period which may have contributed to, but did not account for, the secular trend. The outcome according to pregnancy order (Table 4) suggested an increase in spontaneous abortions and a decrease in perinatal deaths with increasing parity but neither trend was significant at the 5% level.

Since previous observations in Jamaica demonstrated a much lower fetal wastage among deliveries at the University Hospital compared to those elsewhere (Anderson 1971), the outcome by place of delivery was also examined. The site of spontaneous abortions was arbitrary so this analysis was confined to the 538 pregnancies reaching viability of which the site of delivery was known in 452 (84%). There was an overall perinatal death rate among these of 13%, of which the rate for the University Hospital was 15%, for other institutions 13%, and for home deliveries, 11%.

There were eight twin pregnancies in eight women resulting in 14 live children and two stillbirths. Two pairs of twins occurred in the first pregnancy, four pairs in the second, and one pair in the fifth and sixth pregnancies.

Gestational age of live and stillbirths varied from 5 months to full term although the proportion of live births at each month of gestation increased, as expected, with advancing maturity. Stillbirths, as a proportion of total deliveries at each gestational age, fell from 93% at 6 months, to 41% at 7 months, 34% at 8 months, and 4% at full term.

The mode of delivery was recorded in 417

Table 4. Outcome of pregnancy in women with homozygous sickle cell disease (SS) according to pregnancy order

Pregnancy	*n*	Induced abortions	Spontaneous abortions		Stillbirths		Live births	Early neonatal deaths		Perinatal death rate**	Overall fetal wastage*
			No	(rate)*	No.	(rate)**		No	(rate)***		
First	287	8	29	(104)	33	(132)	217	15	(69)	192	276
Second	172	9	22	(135)	18	(128)	123	4	(33)	156	270
Third	97	4	12	(129)	10	(123)	71	4	(56)	172	280
Fourth	45	3	7	(167)	4	(114)	31	0	—	114	262
Fifth	21	1	0		2		18				
Sixth	6	0	1		0		5				
Seventh	3	0	1		0		2				
Eighth	2	0	0		1		1				
Ninth	2	0	0		1		1				
Total	635†	25	72	(118)	69	(128)	469	23	(49)	171	269

† Number of completed pregnancies with known outcome excluding twin pregnancies
* Rate per 1000 pregnancies, ** rate per 1000 births, *** rate per 1000 live births.

deliveries and was by the vaginal route in 358 (86%) and by caesarean section in 59 (14%). The rate for caesarean sections increased from 9.7% in the 15–19 year age group, to 11·9% in the 20–24 year age group, and to 21·9%, in the 25–29 year age group. The caesarean section rate for women with SS disease at the University Hospital, 34/144 (24%), was nearly twice as high as that observed in similar women at four peripheral hospitals, 21/162 (13%). These numbers compare with an overall caesarean section rate of 348/2761 (12·6%) among the general population at the University Hospital, in 1984. Of the 34 caesarean sections in women with SS disease performed at the University Hospital, the indications were fetal distress in 22, cephalo-pelvic disproportion in six, and failure to progress in six. The diagnosis of fetal distress was based on continuous fetal heart monitoring, facilities for which were not generally available outside the University Hospital, so this indication might be expected to occur less frequently elsewhere. However, the lower caesarean section rate in women with SS disease at other institutions was not attended by any discernible increase in fetal mortality.

Birthweights, recorded in 291/469 (62%) of singleton live deliveries, gave a mean of 2·72 (SD 0·63) kg, compared to the mean for all deliveries at the University Hospital in 1984 of 3·11 (SD 0·55) kg. The proportion with a birthweight below 2500 g was 91/291 (31%) among women with SS disease compared to 259/2539 (10·2%) among the normal population delivered at the University Hospital in 1984. Among children born to women with SS disease, birthweights were significantly and positively correlated with gestational age and also with neonatal mortality, children dying within the first week of life having significantly lower birthweights (mean 2·09, SD 0·94 kg) compared with survivors (mean 2·75, SD 0·60 kg). After allowing for gestational age, birthweight was not found to be influenced by maternal age or year of delivery, but there was a small increase in weight with parity, showing an average increase of 82 g (SEM 31 g) for each successive baby up to the third delivery.

Maternal mortality was associated with pregnancy in seven women and a further two patients were pregnant when last seen and were known to have died either during pregnancy or within one year of delivery. Details of the seven confirmed deaths associated with pregnancy are presented in Table 5. Expressing maternal mortality as a proportion of total pregnancies in each secular period, there was a rate of 0·6% for 1970–1974, 1·0% for 1975–1979 and 2·5% for 1980–1984.

Discussion

There is general agreement on an increased fetal wastage in mothers with SS disease although there is conflicting information on the stage of pregnancy at which fetal loss occurs.

Milner *et al.* (1980) reported an abortion rate of 19·2% and noted the close agreement of this figure with that reported by Eisenstein *et al.* (1956) and that derived from a review of the literature since 1956. The overall abortion rate

Table 5. Summary of pregnancy-related maternal deaths in seven women with homozygous sickle cell disease

No	Age (years, months)	Pregnancy	Year of death	Time of death	Autopsy	Findings (clinical if no autopsy)
1	19 years 10 months	1	1975	4 days post partum	No	(Dyspnoea, restlessness, vomiting). ? Pulmonary embolism
2	20 years 4 months	1	1983	8 months gestation	Yes	Severe bilateral bronchopneumonia
3	20 years 7 months	1	1981	1 day post partum	Yes	Massive pulmonary embolism
4	25 years 7 months	4	1977	3 days post partum	Yes	Pulmonary micro-emboli (painful crisis, jaundice+++)
5	28 years 6 months	2	1974	5 months gestation	No	(Collapsed and died suddenly)
6	31 years 7 months	4	1980	5 days post termination	Yes	Peritoneal haemorrhage following laparoscopic tubal ligation
7	33 years 7 months	3	1981	1 day post partum	No	(Cardio-respiratory collapse)

in the present study was 11·8% although rates of 12·9% and 16·7% occurred in the third and fourth pregnancies respectively. A low abortion rate (9·4%) was reported in a previous Jamaican series (Anderson 1971).

There is no obvious reason for the apparent discrepancy in abortion rates between Jamaican and North American experience, although the significance of missed periods may have been interpreted differently. In Jamaican patients with SS disease, menstrual irregularities are not uncommon and a single missed menstrual period was not considered an abortion unless the menstrual flow of the following period was particularly heavy or there were products of conception. Different definitions of abortion could also have contributed to this difference. Furthermore the pattern may also vary, Milner *et al.* (1980) noting 22% abortions in the first pregnancy but only 9·4% in the second whereas in the present series there was a consistent, though not significant increase in abortions with successive pregnancies.

The stillbirth rate in different series shows less variability. Milner *et al.* (1980) noted stillbirths in 9·1% of viable births and found a rate of 13·9% in a review of the literature. Both rates are comparable with an overall stillbirth rate of 12·8% in the present series.

The significant increase in abortion and stillbirth rates during the period studied was an unexpected finding and open to several interpretations. One possibility was that more comprehensive recording of pregnancy details over the last few years led to a more complete recall of abortions and stillbirths. However, this was not borne out by analyses comparing the groups with and without recent verification of data which indicated that the secular trend persisted even in the group where direct questioning should have led to more complete recall of abortions and stillbirths. It is unlikely that there has been a true deterioration of obstetric performance and the most plausible explanation is a greater survival of high-risk,. severely affected patients to reproductive age, and a greater chance of such patients becoming pregnant.

The pathological basis of the increased abortion and stillbirth rates is unclear. Vaso-occlusion on the maternal side of the placenta is likely to lead to placental infarction and a reduced placental volume which is unable to satisfy the metabolic exchange and growth requirements of the enlarging fetus. It is difficult to envisage a similar mechanism interfering with trophoblast function and causing abortion. More may be learnt about the mechanisms by a study of clinical and haematological risk factors in patients with a history of abortions and stillbirths.

Neonatal deaths are also increased in women with SS disease. Hendrickse *et al.* (1972) reported neonatal deaths in 8/62 (13%) of live deliveries in Ibadan, and in what must be considered highly atypical for North American experience, Fort *et al.* (1971) noted neonatal deaths in 14/64 (22%). Excluding these series, the neonatal death rate in the literature since 1956 reviewed by Milner *et al.* (1980) was 4·0%, similar to the 5·1% observed in the present study. A factor contributing to this increase in neonatal deaths in likely to be the low birthweight of children born to SS mothers and a direct relation between low birthweight and neonatal death was observed in the present study. The genotype of these infants, although more likely to be SS, was extremely unlikely to have been relevant to neonatal deaths since symptoms of SS disease are rare during this period.

Estimates of total fetal wastage in previous reports have varied widely between 20 and 50%. Anderson (1971), reviewing earlier Jamaican experience, noted an overall fetal wastage of 26% but found a lower rate among women delivered in the Unversity Hospital (16%) than in those delivered at home or in other hospitals (41%). This differential in total fetal wastage between institutions was no longer apparent in the present study. The observation that overall fetal wastage in the period covered by the present study was similar to that in the period 1957–1969 (reviewed by Anderson 1971) appears to conflict with the significant increase in both abortions and stillbirths noted between the 1970–1974 and the 1980–1984 periods. But the high rates, especially in the 1980–1984 period, are based on smaller numbers than in the 1975–1979 period and the trend for increase in abortions and stillbirths has been offset, to some extent, by declining neonatal deaths.

A major finding in the present study was the observation of at least seven pregnancy-related deaths. Four occurred in the immediate post partum period and are likely to have been attributable to pulmonary embolism. One was attributable to a surgical accident during tubal ligation and two occurred during pregnancy. In an additional two patients, death occurred in the same year as pregnancy although the exact relation of the two events was unknown. The occurrence of seven deaths in a total of 643 completed pregnancies represents a pregnancy mortality rate of 1·1%, similar to the 1·6% observed in the review of the literature by Charache *et al.* (1980).

The secular trends apparent in this analysis were surprising. There was no consistent improvement in obstetric performance as might have been anticipated from improving standards of medical care but this observation is difficult to interpret because of the changing characteristics of the patient population. There can be little doubt that overall survival of patients with SS disease is improving with the result that more severely affected patients are surviving and reaching reproductive age. Such patients might be expected to have a poorer obstetric performance and this is compatible with both the increasing abortion and stillbirth rates and the high rate of maternal mortality. Despite this trend, however, 77% of pregnancies in women with SS disease resulted in live deliveries.

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The aetiology of preterm labour

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Summary. Factors associated with spontaneous preterm birth were analysed in 254 primigravidae who gave birth to singleton infants between 28 and 36 completed weeks gestation in Aberdeen City District between 1978 and 1982. In 144 women labour followed premature rupture of the membranes and in 110 the membranes were intact and labour began with contractions. Among those with intact membranes, unmarried women and teenagers were over represented to a significant extent compared with all primigravidae. Among those with premature rupture of the membranes, the distribution of age and marital state was similar to that in all primigravidae, but the birthweight centile distribution showed a significant shift towards light-for-dates babies. It is argued that there may be two distinct categories of pregnancies that end in spontaneous preterm labour.

A number of factors have been shown to be associated with spontaneous preterm birth. These include low maternal age and weight, smoking, low social class, illegitimacy, threatened abortion, antepartum haemorrhage, and a past history of abortion, stillbirth or low birthweight infants (Fedrick & Anderson 1976). Preterm delivery has also been associated with an excess of male infants (Hall & Carr-Hill 1982).

The results of many earlier studies are difficult to interpret due to lack of differentiation between spontaneous and induced labour. Even when spontaneous preterm labour has been considered separately, the different modes of onset of spontaneous labour (i.e. premature rupture of membranes, contractions with intact membranes or bleeding) have not been taken into account. It is possible that the mechanisms of onset of labour may differ with different modes of onset and hence the distribution of the various associated social and epidemiological factors could also be different. A study of preterm delivery in twin pregnancies found a difference in monozygosity and the infant sex ratio between infants born after premature rupture of membranes and those born after contractions with initially intact membranes (MacGillivray *et al.* 1982).

The present study was undertaken to compare the distribution of maternal age, social class, marital state, weight, smoking habits, the sex and birthweight of the infant and past history of abortion in women in whom spontaneous preterm delivery followed premature rupture of membranes with that in women in whom delivery followed premature contractions with initially intact membranes. Only primiparae were considered, because of the possible confounding effects of previous abnormal pregnancies (Fedrick & Anderson 1976) and women with antepartum haemorrhage, fetal abnormalities, intrauterine death or multiple pregnancy were excluded, as these are clearly distinct from unexplained preterm labour (Arias & Tomich 1982).

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Subjects and methods

From the records of all patients delivered in Aberdeen City District between 1978 and 1982, all primigravidae and virtual primigravidae (i.e. those without a previous viable pregnancy) who were delivered of a singleton infant between 28 and 36 completed weeks gestation were selected. The case notes of these women were reviewed retrospectively for maternal age, marital state, height, weight, social class, smoking habit, previous abortions, complications of the present pregnancy, gestation at delivery, birthweight and sex of infant. Gestation at delivery was calculated as the number of completed weeks from the first day of the last menstrual period. The gestational age was considered to be certain only when the date of the last period was remembered to within 1 week and the menstrual cycle had been regular without the use of hormonal contraception in the cycle before conception. When approximate dates (i.e. accurate to within 2 weeks) were corroborated by ultrasound and clinical examination, the gestational age was also considered to be certain. In this study all other cases were considered to be of uncertain gestation (Hall *et al.* 1985).

Birthweights were corrected for sex of infant, maternal height and midtrimester weight using the standards of Thomson *et al.* (1968) and the

Table 1. Uncertain gestation and previous abortion by state of membranes at onset of labour in women delivered after preterm labour

		Uncertain dates		Previous abortion	
State of membranes at onset	*n*	*n*	(%)	*n*	(%)
Intact	110	33	(30)	18	(17)
Ruptured	144	23	(16)	39	(27)

Table 2. Distribution of social factors by state of membranes at onset of labour in preterm births and in total primigravid population

	Spontaneous preterm delivery				Total primigravid population (n = 2243)	
	Intact membranes (n = 110)		Ruptured membranes (n = 144)			
Social factors	*n*	(%)	*n*	(%)	*n*	(%)
Age (years)						
<20	47	(43)	27	(19)	428	(19)
20–29	50	(45)	100	(69)	1589	(71)
>30	13	(12)	17	(12)	226	(10)
	χ^2 = 18 4 (P<0·001)					
Marital state						
Married	71	(65)	123	(85)	1780	(81)
Single	39	(35)	21	(15)	406	(19)
	χ^2 = 15·1 (P<0·01)					
Social class						
I + II	18	(16)	38	(26)	463	(21)
III	31	(28)	42	(29)	865	(41)
IV + V	15	(14)	28	(19)	532	(24)
Unclassified	40	(36)	23	(16)	234	(10)
Unknown	6	(6)	13	(9)	79	(4)
	χ^2 (for trend) = 0·14 (NS)					
Smokers	57	(52)	64	(44)	1023	(46)
Non-smokers	53	(48)	80	(56)	1200	(54)
	χ^2 = 1·37 (NS)					

Table 3. The marital state in different age groups by state of membranes at onset of preterm labour

		State of membranes			
		Intact		Ruptured	
Age (years)	Marital state	*n*	(%)	*n*	(%)
<20	Married	21	(45)	17	(63)
	Single	26	(55)	10	(37)
Total		47	(100)	27	(100)
		$\chi^2 = 2{\cdot}30$ (NS)			
≥20	Married	50	(79)	106	(91)
	Single	13	(21)	11	(9)
Total		63	(100)	117	(100)
		$\chi^2 = 4{\cdot}47$ ($P<0{\cdot}05$)			

birthweight centiles were calculated for infants born at or after 32 completed weeks (birthweight standards being unavailable before this gestation).

The distribution of maternal age, marital state, social class, smoking, maternal height, weight, previous abortion (spontaneous or induced), uncertain gestation, birthweight centile and sex of infant were compared between women delivered after premature rupture of membranes and those in whom contractions began with intact membranes. Differences in distribution were assessed for statistical significance using the χ^2 test and were also compared with the overall distribution of the same factors in all primigravidae and virtual primigravidae delivered in Aberdeen City District between 1980 and 1982.

All analyses were repeated after excluding women with uncertain gestational age or a past history of abortion.

Results

There were 357 singleton preterm births in primigravidae and virtual primigravidae in the period under study. Women were excluded from the study for the following reasons· induced labour ($n = 20$), elective caesarean section ($n = 34$), delivery after antepartum haemorrhage ($n = 35$) and intrauterine fetal death ($n = 24$). Ten women had more than one reason for exclusion so that 103 were excluded, leaving a total of 254 who were delivered of live infants after uncomplicated spontaneous preterm labour. Of these 254 women, 110 started contracting with intact membranes and 144 started contracting after premature rupture of membranes (PROM group) (Table 1). Of the six women with intra-uterine deaths whose labour started spontaneously, all started contracting with intact membranes. The age distribution of women presenting with PROM was similar to that of the primigravid population as a whole, 19% were <20 years of age. In contrast 43% of the women with intact membranes at the onset of labour were <20 years of age. The difference in age distribution was statistically significant ($P<0{\cdot}001$) (Table 2).

There was also a much greater proportion of unmarried women in the intact-membranes group ($P<0{\cdot}01$). Again the PROM group had a distribution close to that seen in the overall population. When age and marital state were analysed together (Table 3) the expected association of youth and unmarried state was found, but there was still a higher proportion of single women in the intact-membranes group both in teenagers and older women. Similarly, there was still a higher proportion of women aged under 20 in the intact-membranes group irrespective of marital state. This suggests that marital state and age are separate variables (Table 3).

Social class distributions showed an increase in social classes I and II in the PROM group. The larger numbers of unclassified social class in the intact-membranes group is due to the larger number of unmarried women in this group. When the unclassified women were excluded from the analysis, the differences in social class distribution between the two groups were not statistically significant and this was also the case when differences in smoking habit, maternal height and weight were considered.

Table 4. Sex of infants by state of membranes at onset of preterm labour

State of membranes	Male	Female	Male·female ratio
Intact	59	51	1·15
Ruptured	71	73	0 97
	χ^2 = 0·313 (NS)		

Table 5. Distribution of birthweight centiles by state of membranes at onset of labour in women delivered between 32 and 36 completed weeks

	State of membranes			
Birthweight centile	Intact (n = 69)		Ruptured (n = 106)	
	n	(%)	n	(%)
0–10	6	(9)	17	(16)
11–25	8	(12)	20	(19)
26–50	20	(29)	44	(41)
51–75	23	(33)	14	(13)
76–90	10	(14)	8	(7)
91–100	2	(3)	3	(3)
	χ^2 (for trend) = 9·127 (P<0 01)			

The sex ratio at birth differed between the two groups but the difference was not statistically significant (Table 4).

Birthweight centile analysis showed a tendency for those infants in the PROM group to be lighter for dates than those born in the intact-membranes group (P<0·01) (Table 5). As birthweight centiles could only be determined for the babies with certain gestational age and after 32 completed weeks of gestation, the numbers in Table 5 are less than in the earlier analysis. A smaller than expected proportion of infants above the 90th birthweight centile was observed in both groups. This trend was also reported by Carr-Hill & Pritchard (1983) and probably reflects a change in the population of births since the original birthweight standards were formulated.

In the intact-membranes group the proportion with uncertain gestation was greater and the proportion with previous abortion was smaller than in the PROM group (Table 1). However, when those women with uncertain gestation and previous abortion were excluded, the differences in distribution of the other factors was unchanged and remained statistically significant.

Discussion

With the exception of Arias & Tomich (1982) previous studies of the epidemiology, aetiology and outcome of spontaneous preterm labour have not differentiated between these two modes of onset. Our study has identified an over representation of single and teenage women in the group starting preterm labour with intact membranes and a shift towards low birthweight for gestational age in the group starting with premature rupture of the membranes. The differences between these two groups in respect of these factors suggests that these two forms of

Table 6. Distribution of maternal age and marital state by state of membranes at onset of preterm labour (previous abortions excluded)

	State of membranes			
	Intact (n = 92)		Ruptured (n = 105)	
	n	(%)	n	(%)
Age (years)				
<20	42	(46)	23	(22)
20–29	8	(41)	71	(68)
30+	12	(13)	11	(11)
	χ^2 = 14·74 (P<0·01)			
Marital state				
Married	58	(64)	88	(84)
Single	34	(36)	17	(16)
	χ^2 = 11·02 (P<0·01)			

Table 7. Distribution of maternal age and marital state by state of membranes at onset of preterm labour (uncertain gestation excluded)

	State of membranes			
	Intact (n = 77)		Ruptured (n = 121)	
	n	(%)	n	(%)
Age (years)				
<20	29	(38)	19	(16)
20–29	38	(49)	89	(74)
30+	10	(13)	13	(11)
	χ^2 = 13·97 (P<0·01)			
Marital state				
Married	58	(75)	107	(88)
Single	19	(25)	14	(12)
	χ^2 = 5·82 (P<0·02)			

Table 8. Distribution of birthweight centiles by state of membranes at onset of labour in women delivered between 32 and 36 completed weeks (previous abortions excluded)

Birthweight centile	State of membranes: Intact (n = 56)		Ruptured (n = 74)	
	n	(%)	n	(%)
<10	5	(9)	13	(18)
11–25	6	(11)	11	(15)
26–50	18	(32)	35	(47)
51–75	17	(30)	8	(11)
76–90	8	(14)	5	(7)
91–100	2	(4)	2	(3)

χ^2 (for trend) = 6·12 (P<0·02)

preterm labour represent two different pathological processes. These observations can be interpreted in several ways. The over representation of unmarried and teenage women in the intact membrane group suggests either that young and single women are in some way predisposed to preterm uterine contractions or that another factor is involved which is commoner in pregnancy in young and single women and also predisposes to preterm labour with intact membranes. The lower birthweights for gestational age found in the PROM group could be interpreted in three ways. First, smaller fetuses may in some way cause the membranes to rupture; second, premature rupture of the membranes may cause the fetus to stop growing and thus be smaller and third, another unknown factor may be involved which predisposes to premature membrane rupture and also leads to reduced fetal growth.

The aetiology of spontaneous preterm labour is not clearly understood. One commonly held belief is that premature contractions may start as a mechanism for delivery of a distressed fetus. If this were the case, those labours starting with intact membranes would be expected to produce more growth-retarded babies. The present study has shown the opposite. It is, however, of interest that all six women in whom intrauterine death was followed by spontaneous onset of labour, started the labour with intact membranes.

Maternal infection, either intrauterine or extrauterine, may also predispose to preterm labour (Naeye & Peters 1978). We have found no published evidence that infections are more common in single, teenage girls than in married women. In our retrospective study, it was not possible from the data available to determine the frequency of infection in the two groups.

Intrauterine infection may be more common with more frequent coitus (Naeye 1979). Other workers have suggested an association between orgasm and the onset of labour (Goodlin 1971). Although it is possible that the difference between the two groups was due to a difference in coital habits, we have no information on coital frequency in our study. It is also difficult to explain the difference in birthweight distribution on this basis.

Maternal stress has been shown to be higher in women who start labour preterm (Newton *et al.* 1979). These workers assessed stress by using a modified Life Events Inventory and from study of the inventory it is probable that single teenagers would experience more stressful life events than married women. This may explain the larger number of single teenagers in the intact membrane group. However, Newton *et al.* (1979) did not differentiate the two modes of onset of preterm labour.

Premature rupture of membranes may be due to a decreased elasticity or tensile strength of the membranes (Parry Jones & Priya 1976). It is possible that membranes of a smaller baby may be less elastic. Although Polishuk *et al.* (1964) showed that in term pregnancies the tensile strength of membranes tested *in vitro* was greater when the birthweight was less, there is no information relating elasticity of membranes to birthweight in women with premature rupture.

An explanation for the differences between these two groups has not been found. The important conclusion is that these two forms of spontaneous preterm labour involve different groups of pregnancies. Studies in the past have often failed to distinguish between the two groups and therefore conclusions regarding aetiology, management and prognosis are difficult to interpret. In a similar way that division of the old classification 'prematurity' into preterm and light-for-dates babies helped to clarify the causes and management of low-birthweight infants, division of spontaneous preterm births into two groups according to the state of the membranes at the onset of labour may help to clarify the problem of preterm labour.

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Pain relief in labour using transcutaneous electrical nerve stimulation (TENS). A TENS/TENS placebo controlled study in two parity groups

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Summary. The analgesic effects of transcutaneous electrical nerve stimulation (TENS) in labour and effects on outcome were investigated in a double-blind TENS/TENS placebo controlled trial in 100 primigravidae and 50 women in their third labour. There were no differences between the TENS and the TENS placebo users in terms of pain concept or relief, and only 12 and 13% of primigravidae and 48 and 39% of the para 2 women completed labour without requiring other analgesia in their respective groups. The primigravidae who used either TENS or TENS placebo alone had shorter labours than those who required further analgesia. Although the outcome of labour for mother and infant were similar in the two groups, there was a higher operative delivery rate in women who also had epidural analgesia. There were highly significant differences between the TENS and the TENS placebo users in terms of favourable and unfavourable comments by the mothers and the midwives at 1 and 24 h after delivery. The evident consumer satisfaction for TENS suggests TENS has a part to play in analgesia in labour but the equivocal findings in terms of factors associated with pain relief points to the need for apparatus more specifically designed to cope with the special characteristics of the pain of labour.

Pain relief poses a major problem in labour. The present methods of analgesia appear to meet the needs of most parturients but are not without contra-indication and complication (Crawford 1984). There is clearly room for improvement and more particularly the development of a self-administered method that is effective, non-invasive, allows ambulation and which would interfere minimally with the chances of a safe spontaneous natural vaginal delivery.

The quest for such an advance led us to investigate the use of transcutaneous electrical nerve stimulation (TENS). This method of analgesia is used for chronic pain relief in other branches of medicine (Lewith 1983) Post square wave electrical current is applied through surface electrodes placed on the skin. Analgesia is achieved, it is theorized, either by blocking pain impulses to the brain by increasing A-fibre transmission (the so-called gate theory of Melzak and Wall (1965)), or by stimulating the local release of endorphins (Sjolund *et al.* 1977).

TENS has been shown to be safe during

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labour (Bundsen & Ericson 1982), with no effect on the newborn infant (Bundsen *et al.* 1982*a*). Various degrees of pain relief have been reported in the few studies published to date (Shealy & Maurer 1974; Robson 1979; Stewart 1979). The largest series was a Scandinavian study (Bundsen *et al.* 1981) which also demonstrated possible advantages in outcome for mother and fetus. Placebo controlled obstetric studies are few (Neumark *et al.* 1978; Nesheim 1981) although Lewith (1983) noted a 30% positive response to TENS placebo in patients with chronic pain and the response to active TENS in other clinical situations has been shown to be greater than to sham stimulation (Jeans 1979).

As TENS has the potential to satisfy the necessary criteria for an ideal method of analgesia in labour, a double-blind study was embarked on at the Rotunda Hospital Dublin, comparing the efficacy of TENS in labour with that of TENS placebo (TPL). This initial report describes the findings in women having a first or third labour. The former were selected because it was their first experience of labour and the latter as they would have already experienced two previous different labours.

Subjects and methods

Patient selection

Primigravid women and those in their third labour admitted to the main labour ward, Rotunda Hospital Dublin, between June and December 1983 were asked if they had already decided upon a specific form of analgesia. Those who had not were given a simple explanation of the mechanics of TENS by the midwife in charge. The patient was assured that she would be instructed in its use until confident, that the use of TENS did not exclude using additional analgesia and that all current forms of analgesia would also be available. Patients were informed of the nature of the TENS/TPL control study and 100 primigravidae and 50 parous women (para 2) who all gave informed consent were admitted to it.

Apparatus

Two pairs of carbon rubber electrodes were placed on either side of the spine approximately 5 cm from it. Application sites were moistened so as to improve conductivity and adhesion. Mindful of the dermatome distribution and the sites of pain usually experienced in labour the upper pair of electrodes (disposable) were placed to cover the dermatomes of the posterior rami from T10 to L1 inclusively. The smaller lower pair (re-usable) covered dermatomes of the posterior rami from S2 to S4. These electrodes were attached to either an active or placebo, Tenzcare Dual Channel Stimulator Model 6240 (3M Minnesota St Paul, USA) one of six. Three of these machines functioned optimally but the remaining three were inactive TENS-placebo machines (the red light functioned but there was no power).

Each machine was set initially with a pulse width (duration) of 3 to 4 (60–80 μs) and a pulse repetition rate preset to 5 to 6 (80–100 pulses per second (pps)). Patients were instructed and allowed to adjust the amplitude settings to gain analgesic relief commencing with 5 on both channels increasing gradually as the contractions gained momentum to higher amplitudes and density. Patients well advanced in labour were found to benefit from the pulse burst mode (2 burst per second, 7 pulses per burst, 100 pps intraburst rate) facility on the R dial of the machine.

Treatment allocation

Patients were allocated randomly to one of the six numbered machines. Neither patient nor midwife knew which were active and placebo machines. Numbering was changed at regular intervals by a third party to try and avoid the possibility of exposing the double-blind cover. For the same reason patients were not made aware that they should experience any sensation at the site of the electrodes

Of the 100 primigravidae 49 used active TENS and 51 the placebo TENS; of the 50 parous women 27 used TENS and 23 the placebo.

Pain assessment

Labour was managed by the regular staff in the usual manner. Specific data collected included an initial assessment of pain threshold as measured by a Monsanto Gun (Table 1), an hourly assessment throughout labour by the patient of her pain and its sites on a scale rated from 0 (no pain) to 4 (very severe pain), with the research midwife also giving her assessment of the site and amount of pain relief on a 0 (nil) to 4

Table 1. Initial pain threshold

Pain threshold* (kg/cm²)	Para 0		Para 2	
	TENS	TPL	TENS	TPL
≤2	0	2	0	0
2–4	26	24	1	4
4–6	20	21	20	15
>6	3	3	6	4
Total	49	50	27	23

* Measured by a Monsanto gun.

TENS, Transcutaneous electrical nerve stimulation; TPL, TENS placebo.

(excellent) scale. These events and others such as the introduction of different analgesia were related in time to the onset of labour and to dilatation of the cervix.

All details of the birth were recorded including condition of the baby as measured by cord blood pH and Apgar scores at 1 and 5 min. One hour and 24 h after delivery, the patients were asked for their comments regarding the method of analgesia. Particular note was made of pain relief, site of relief, and any other favourable or unfavourable comments. They were also asked whether they would request TENS again. The attendant midwife recorded her assessment of the pain relief apparently achieved by the patient, its sites, the merits and demerits of TENS and the presence of any side effects that could be ascribed to the treatment.

Data processing and statistical methods

Data were collected, tabulated and computerized for further analysis. An initial check was made on factors that might introduce intergroup bias thus preventing valid direct comparison between the women using TENS and those using the TENS placebo.

Both the relevant groups of primigravidae and para 2 women using TENS or placebo TENS were comparable in terms of age, marital and socio-economic status and attendance at antenatal classes. During labour there were no differences in the number of patients who were induced, methods of induction that were used or numbers accelerated by artificial membrane rupture or oxytocin. Table 1 shows that the distributions of the initial pain threshold measurements were almost identical in the respective TENS and TPL groups as were the pain scores at time zero (Table 2), the onset of the study before analgesia.

The validity for comparison thus established, the efficacy of TENS and TPL in both parity groups was then examined. Pain assessments, other analgesia, the outcome of labour and the comments of patients and midwives after delivery were analysed in the four groups.

Chi-squared (χ^2) tests were used for assessing the significance of contingency tables. Differences in time to requiring further analgesia and in cervical dilatation at that time were analysed using Cox's models (Cox 1972) for survival analysis with covariates. Cases requiring no further analgesia were assumed to have times greater than their delivery time and dilatation ≥10 cm respectively.

Results

Pain assessment during labour

In both parity groups there were no significant differences between the TENS and TPL users in terms of either the patients' concept of pain or the midwives' assessment of pain relief at any of the hourly intervals measured. Table 2 shows pain scores at times zero and 1 h (respectively $P \geq 0{\cdot}1$, χ^2).

The vast majority of patients in all groups experienced pain in the suprapubic and lower back regions initially. Again no inter-group

Table 2. Pain score at times zero and 1 hour

Pain score*	Para 0				Para 2			
	TENS		TPL		TENS		TPL	
	0	1 h	0	1 h	0	1 h	0	1 h
0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	1	0
2	5	0	9	1	8	1	4	3
3	33	17	28	11	15	8	14	2
4	11	29	14	34	4	9	4	8
Total	49	46	51	46	27	18	23	13

* 0 = Nil to 4 = Severe

TENS, Transcutaneous electrical nerve stimulation, TPL, TENS placebo.

Scores were collapsed as appropriate because of small expected frequencies. TENS and TPL para 0 and para 2 at 0 and 1 hour respectively χ^2 = NS ($P \geq 0{\cdot}1$)

Table 3. Analgesia used in addition to either TENS or TPL

	Para 0		Para 2	
Additional analgesia	TENS (n = 49)	TPL (n = 51)	TENS (n = 27)	TPL (n = 23)
None	6	7	13	9
Entonox	14	5	9	6
Pethidine and sparine	9	8	3	4
Epidural	9	13	2	1
Pethidine and sparine + Entonox	7	6	—	3
Pethidine and sparine + Epidural	4	12	—	—

TENS, Transcutaneous electrical nerve stimulation; TPL, TENS placebo

differences were noted as labour progressed. No site of pain was better relieved than another or with TENS compared with TPL.

Other analgesia

Table 3 shows that the percentages of primigravidae who completed labour without requiring further analgesia were only 12 and 14% in the TENS and TPL groups respectively. In the para 2 women the respective percentages rose to 48 and 39%. There were no significant differences between any subgroups regarding numbers requiring further analgesia or when it was first given in relation to duration of labour or cervical dilation (Cox's models).

At the Rotunda Hospital, self-administered Entonox (nitrous oxide and oxygen) is a method of analgesia routinely accepted by many women entering the second stage of labour. If the use of Entonox is disregarded, the proportion of primigravidae not requiring any other analgesia rose to 41% and 24% in the TENS and TPL groups respectively and in the para 2 women to 81% and 65% respectively. However, the present study was intended to compare TENS and TPL not TENS + Entonox with TPL + Entonox. Nevertheless, it is interesting to note that fitting log linear models to these data show that the women treated with TENS + Entonox were significantly less likely to require further analgesia than those treated with TPL + Entonox (P = <0·0001, P = <0·025 respectively).

Table 4 shows that the duration of labour was shorter in the primigravidae who used either TENS or TPL alone than in those needing further analgesia. Two-way analysis of variance of these patients using factors TENS/TPL and whether or not patients had further analgesia showed that patients who did not require further analgesia had significantly shorter labours (P = <0·005). There were, however, no significant differences between the TENS and TPL users in the para 2 groups or when the relevant Entonox users were added to the TENS and TPL users in either parity group.

Outcome of labour

Table 5 shows that there were no real differences in the occurrence of normal and operative deliveries between TENS and TPL users either in the primigravidae or the para 2 patients. Table 6 shows that all the women who used either TENS or TPL alone had normal deliveries. However, of the 38 primigravidae who also chose an epidural only three of the 13 TENS users and eight of the 25 TPL users had a non-operative delivery. There were no significant differences in Apgar scores between the groups at 1 or 5 min. The mean cord blood pH values were also almost identical in the four groups (Primigravidae: TENS 7·3, SD 0·07; TPL 7·23, SD 0·06. Para 2: TENS 7·25, SD 0·06; TPL 7·25, SD 0·06).

Table 4. Hours of labour and analgesia used in addition to either TENS or TPL

	Para 0		Para 2	
Additional analgesia	TENS	TPL	TENS	TPL
None	6·2 (2·7) (n = 6)	5·0 (1·5) (n = 7)	4·9 (2·2) (n = 13)	4·3 (2·5) (n = 9)
Various	8·5 (3·1) (n = 43)	7·9 (2·4) (n = 44)	4·7 (2·0) (n = 14)	4·8 (2·1) (n = 14)
Entonox	7·4 (2·7) (n = 20)	5·7 (1·5) (n = 12)	4·7 (2·2) (n = 22)	4·0 (2·0) (n = 15)
Various + Entonox	8·8 (3·3) (n = 29)	8·1 (2·5) (n = 39)	5·2 (1·1) (n = 5)	5·8 (2·2) (n = 8)

Results are means (SD), n = number of patients
TENS, Transcutaneous electrical nerve stimulation, TPL, TENS placebo

Table 5. Mode of delivery

	Para 0		Para 2	
Mode of delivery	TENS	TPL	TENS	TPL
Normal	31	28	24	22
Forceps	13	19	2	0
Vacuum	2	1	1	0
Caesarean section	3	3	0	1
Total	49	51	27	23

TENS, Transcutaneous electrical nerve stimulation, TPL, TENS placebo
$\chi^2 = 0{\cdot}72$, $P = <0{\cdot}25$.
The variable mode of delivery was collapsed over the categories Forceps, Vacuum and Caesarean section for χ^2 tests. No χ^2 performed on para 2 because of expected frequencies of two cells were too low even after collapsing.

Comments after delivery

Favourable and unfavourable comments on the method used are summarized in terms of adequacy, efficacy and the desire to use TENS again as intimated in the answers to a standard set of questions designed to ask specifically about TENS. Related experiences about any other form of analgesia the patient may have had during labour were not included but, as this may have played some part in the satisfaction ratings, the data are analysed not only in terms of TENS and TPL alone, but the responses are also divided according to whether or not further analgesia was given (Table 7).

Table 7 shows that there were highly significant differences in terms of favourable and unfavourable comments both from the midwives and the patients at 1 and 24 h after delivery between the TENS and TPL groups. The primigravid TENS users commented favourably whether or not they had further analgesia. Most of the TPL users who had further analgesia had unfavourable comments, unlike the TPL users who required no further analgesia but their numbers were too small for statistical significance. This overall tendency was more pronounced in the para 2 patients; again the TPL users who required further analgesia appeared the least satisfied.

Discussion

The actual mechanisms that produce pain in labour have not yet been fully determined (Bonica 1975), but during the first stage of labour, pain may be due predominantly to cervical dilatation with contractions of the uterus contributing significantly as labour progresses (Bonica 1979). Repeated stimulation may reduce the high threshold of receptors and contractions may cause cellular breakdown releasing 'pain producing substances'. Pain impulses are transmitted via the A-delta and C-afferent fibres reaching segments T11 and 12. Increasing intensity gives rise to pain referred also to adjacent segments in the region corresponding to dermatome distribution T10 to L1. From full dilatation, extension and stretching of the birth

Table 6. Type of delivery and analgesia used in addition to either TENS or TPL

	Para 0				Para 2			
	TENS		TPL		TENS		TPL	
Additional analgesia	Normal	Op.	Normal	Op.	Normal	Op	Normal	Op
None	6	0	7	0	13	0	9	0
Entonox	9	5	4	1	8	1	6	0
Pethidine and sparine	8	1	6	2	2	1	3	1
Epidural	2	7	2	11	1	1	1	0
Entonox + pethidine and sparine	5	2	3	3	0	0	3	0
Epidural + pethidine and sparine	1	3	6	6	0	0	0	0

Op, Forceps, vacuum or caesarean section
TENS, Transcutaneous electrical nerve stimulation; TPL, TENS placebo

Table 7. Patients and midwives overall comments after delivery with either TENS or TPL and in the subgroups requiring additional analgesia (+A)

	Para 0				Para 2			
	TENS		TPL		TENS		TPL	
Overall comment	Total	+A†	Total	+A†	Total	+A†	Total	+A†
Patients at 1 h								
Favourable	44	38	24	19	26	14	8	2
Unfavourable	5	5	27	25	1	0	15	12
TENS *vs* TPL	$\chi^2 = 21·0$ $P<0·001$				$\chi^2 = 21·6$ $P<0·001$			
Patients at 24 h								
Adequacy								
Favourable	38	32	15	10	22	11	7	1
Unfavourable	11	11	36	34	5	3	16	13
TENS *vs* TPL	$\chi^2 = 23·2$ $P<0·001$				$\chi^2 = 13·3$ $P<0·001$			
Efficiency								
Favourable	45	39	23	18	26	14	7	1
Unfavourable	4	4	28	26	1	0	16	13
TENS *vs* TPL	$\chi^2 = 25·1$ $P<0·001$				$\chi^2 = 26·0$ $P<0·001$			
Would request again								
Yes	30	25	20	13	22	10	10	2
No*	19	18	31	31	5	4	13	12
TENS *vs* TPL	$\chi^2 = 4·8$ $P<0·05$				$\chi^2 = 7·8$ $P<0·01$			
Midwives								
Favourable	44	38	22	17	26	13	7	2
Unfavourable	5	5	29	27	1	1	16	12
TENS *vs* TPL	$\chi^2 = 24·2$ $P<0·001$				$\chi^2 = 24·0$ $P<0·001$			

TENS, Transcutaneous electrical nerve stimulation; TPL, TENS placebo

* includes 'no', 'don't know' and qualified 'yes'.

† The subgroup +A refers to the patients who required further analgesia in addition to either TENS or TPL.

canal activates the pudendal nerves and roots S2-4.

However, the amount of pain actually experienced depends not only on these afferent and efferent pathways but also on the so-called third dimension. This is composed of psychological factors made up of previous experiences, present expectations, stress and cultural factors. In labour not only do these have a profound effect (Nilsson 1970) but they also make measurements of pain experience in studies such as this extremely difficult even when using a double-blind placebo controlled method. It is therefore reassuring to note that in the present study the groups were initially comparable in terms of pain threshold and pain concepts.

Pain relief in labour has been claimed following the passage of low intensity currents through electrodes supplied to the frontal and mastoid regions (Persianinov 1975), acupuncture (Wallis *et al.* 1974), acupuncture plus diazepam (Hyodo & Geger 1977), and electro acupuncture (Kubista *et al.* 1978). Although Neumark *et al.* (1978) found TENS a more effective analgesia than placebo, in a carefully designed study Nesheim (1981) found no differences between TENS and TENS placebo users in the degree of pain relief and in the need for analgesics. Non-controlled studies have, however, been more positive: Shealy & Maurer (1974) reported good effects on back pain and 44% of the patients reported by Augustinnsson *et al.* (1977) found it very good. However 12% found TENS to have no effect, which agrees with the findings of Andersson *et al.* (1976). In the largest study to-date, Bundsen *et al.* (1981) concluded that although TENS had a good effect on back pain with no other effects on mother or child, their post-delivery questionnaire tended to favour TENS but only as a complement to conventional methods.

In the present study, like all others reported to-date, no side-effects were noted from the therapy. In contrast to the studies reported by Augustinnsson *et al.* (1977) and Bundsen *et al.* (1981) we found no interference with electronic monitoring of the fetal heart. We found no difference in pain assessment by patients or midwives during labour between TENS and TPL users. Only few primigravidae completed labour without requiring further analgesia but more para 2 patients did not require further analgesia and if the use of Entonox is disregarded, the proportion requiring no further analgesia was significantly higher in the TENS users. In agreement with Nesheim (1981) we found a relation between the length of labour and the need for further analgesia. Labours were significantly shorter in those primigravidae who required no further analgesia. Bundsen *et al.* (1981) and Kubista *et al.* (1978) considered that such findings show that TENS shortens labour However, as the duration of labour shows a strong positive correlation with pain intensity (Bundsen *et al.* 1982*b*), we feel that a more plausible interpretation is that the use of TENS as the only analgesic is better suited to those having short labours.

The present study confirms that TENS is safe for the infant in terms of Apgar score and umbilical blood pH. The fact that all the patients who used only TENS or only TPL had normal deliveries may be again a reflection of short labours. This contrasts particularly with the higher operative delivery rates in the other groups who needed further analgesia and in particular in those primigravidae who requested epidurals. This might play some part but does not explain completely the surprisingly highly significant differences in favourable and unfavourable comments from patients and midwives between the TENS and TPL users in both parity groups even when the use of other analgesia is taken into account.

Such evident consumer satisfaction therefore suggests that TENS has a part to play in analgesia in labour particularly where labour is likely to be short. However, the equivocal findings in this study, particularly in terms of pain assessment during labour and the necessity for further analgesia in the majority of patients, points to the need for the development and assessment of apparatus more specifically designed to cope with that most intense of all pains (Melzak *et al.* 1981), the progressive pain of labour.

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Fetal sympatho-adrenal mediated metabolic responses to parturition

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Summary. Plasma cortisol and noradrenaline were measured in 15 mothers and babies following vaginal delivery and in 17 following elective caesarean section and related to blood concentration of glucose and glycerol. Significant elevations in umbilical artery cortisol and noradrenaline concentration were found in the vaginal delivery group. Blood glucose and glycerol concentrations were significantly higher in the vaginal delivery group for maternal venous, umbilical artery and vein samples. However, when allowances were made for placental transfer of these substances, little evidence was found to support sympatho-adrenal mediated mobilization of glycerol and glucose in the fetus. The possible explanation for the apparent dissociation between marked sympatho-adrenal activity and metabolic responsiveness during parturition in the fetus is discussed.

Sympatho-adrenal activity causes profound physiological and metabolic responses including glycogenolysis and lipolysis (Young & Landsberg 1977). These biochemical changes include a rise in blood glucose, free fatty acids and glycerol. Previous studies have demonstrated that parturition, especially following labour, causes a profound increase in fetal sympatho-adrenal activity (Lagercrantz & Bistoletti 1977; Falconer & Lake 1982; Irestedt *et al.* 1982). The magnitude of this activity is less following delivery by elective caesarean section (Falconer & Lake 1982; Irestedt *et al.* 1982). Previous work has suggested an apparent dissociation between fetal sympatho-adrenal activity at delivery and lipolytic responsiveness (Falconer 1984).

This study was designed to quantify fetal sympatho-adrenal activity by catecholamine measurements and to relate this to blood glucose and glycerol concentrations in two study groups: a group of mothers and fetuses exposed to labour and vaginal delivery and a separate group delivered by elective caesarean section.

Subjects and methods

Fifteen vaginal deliveries and 17 deliveries by elective caesarean section were included in this study which was approved by the Nottingham District Ethics Committee. Eleven caesarean sections were performed under epidural blockade and six under general anaesthesia. Nine patients had normal vaginal deliveries, four required a forceps delivery (three for delay in the second stage of labour and one for fetal distress), and two had assisted vaginal breech deliveries. Nine labours were induced by artificial rupture of the membranes together with intravenous oxytocin. Ten women received epidural analgesia, the remainder intramuscular pethidine. Indications for caesarean section were breech presentation (6), previous caesarean section (9), small stature (1), and placenta praevia (1).

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Pregnancies included were at least of 37 weeks gestation by menstrual history. The two groups were similar for infant birthweight (Table 1). No patient with known renal, metabolic or fetal disorder was included. No obstetric differences were apparent within the caesarean section group between those delivered under epidural or general anaesthesia.

Maternal intravenous fluids administered were either normal saline (Na^+ 150 mmol/l, Cl 150 mmol/l) or Hartmann's solution (Na^+ 131 mmol/l, K^+ 5 mmol/l, Ca^{++} 1 mmol/l, Cl 111 mmol/l, lactate 29 mmol/l). In two vaginal deliveries intravenous dextrose (anhydrous dextrose 277 mmol/l) was administered: these deliveries were excluded from the analysis of metabolic variables

Maternal blood samples were obtained from an indwelling venflon cannula (via a three-way tap) as close to the moment of delivery as possible. Blood samples were collected from the umbilical cord arteries and vein following delivery, using a double clamped segment of cord.

Blood gas tensions were measured within 15 min using either an Autocal pH/Blood Gas Analyser 613 (Instrumentation Labs Ltd., England) or a Gas Check pH Blood Gas Analyser 938 (AVL, Switzerland). Both instruments were calibrated before use.

The remaining blood was separated in three ways. An aliquot was added to a preweighed volume of 100% perchloric acid. Following centrifugation and separation the supernatant was stored at −20°C. Duplicate estimations of blood glucose and glycerol were made using an automated enzymatic fluorometric technique (Lloyd *et al* 1978). The interassay coefficient for glucose was 5·7% and for glycerol 10%. In this study glycerol was measured rather than free fatty acid as previous work has shown it to be a more reliable indicator of lipolysis (Hull 1975).

Blood for catecholamines was added to EGTA/glutathione and the separated plasma was stored at −80°C. Duplicate measurements were made using HPLC with ecd (Falconer *et al.* 1982).

The remaining blood was separated and stored at −20°C. Insulin was estimated using a double antibody method with iodinated human insulin. The interassay coefficient of variation over the range of 10–30 m-i.u./ml was 10%. Cortisol was measured with an 'in-house' radioimmunoassay, using antibody supplied by Bioanalysis (Cardiff, UK). The interassay coefficient of variation was 11% at 200 nmol/l, 7·1 at 570 nmol/l and 13·1 at 1250 nmol/l. In some cases inadequate sample volumes were available for all assay measurements. For this reason the sample numbers were included in the figures in parentheses.

In view of the distribution of data, non-parametric analysis was used to test the significance of the differences between groups. Linear regression coefficients were calculated using the method of least squares. In view of the placental transfer of glucose and glycerol, relations were examined with respect to umbilical vein-artery blood concentration of these products.

Results

The acid-base measurements were similar in the two groups (Table 2). In contrast, significant differences in noradrenaline and cortisol concentrations were recorded between the two groups (Figs 1 and 2). Vaginal delivery was associated with significantly higher cortisol levels in maternal venous, umbilical artery and vein blood samples. The same trend was demonstrable for noradrenaline, except that in the maternal venous samples no between group difference was recorded. However, inspection (Figs 1 and 2) demonstrated fundamental differences in the relative concentrations of these two hormones. Maternal venous cortisol con-

Table 1. Birthweight, gestational age and 1-min Apgar scores in the two study groups

	Birthweight (kg)	Gestational age (weeks)	Apgar score 1-min
Mode of delivery	Mean (SD)	Median (range)	Median (range)
Elective caesarean sections	3·44 (0·5)		
Epidural	3·67 (0·5)	39 (38–40)	9 (6–10)
General anaesthesia	3·10 (0·3)	39 (37–39)	9 (9–10)
Vaginal delivery	3·58 (0·4)	41 (38–42)	8 (4–9)

Table 2. Maternal venous and umbilical artery and vein blood gases

	Maternal vein	Umbilical artery	Umbilical vein
Elective caesarean section			
pH	7·43 (0·04)	7·32 (0·05)	7·36 (0·04)
$P\mathrm{co}_2$ (kPa)	4·66 (1·25)	7·33 (2·50)	6·00 (1·80)
$P\mathrm{o}_2$ (kPa)	10·60 (5·80)	2·63 (0·96)	4·02 (0·90)
Vaginal delivery			
pH	7·42 (0·07)	7·33 (0·10)	7·37 (0·08)
$P\mathrm{co}_2$ (kPa)	3·64 (0·74)	5·73 (1·70)	5·07 (1 10)
$P\mathrm{o}_2$ (kPa)	9·62 (2·20)	2·96 (0·88)	3·85 (0·74)

Results are means (SD).

centrations were higher than umbilical artery levels in all deliveries; the reverse was found for noradrenaline. In addition, umbilical artery noradrenaline concentrations were higher than vein levels in all cases. For cortisol, vein concentrations were higher in seven cases.

Blood glucose and glycerol concentrations were significantly higher in the vaginal delivery group for maternal venous, umbilical artery and vein samples (Table 3). In contrast, no between group differences were recorded for plasma insulin. In the caesarean section group a positive relation was found between vein – artery glucose and maternal glucose concentration ($r = +0{\cdot}63$, $P<0{\cdot}001$). No such relation was demonstrable in the vaginal delivery group (Fig. 3). In addition, in the caesarean section group, a linear relation was found between umbilical artery noradrenaline and vein–artery blood glucose (Fig. 4). No such relation was found in the vaginal delivery group.

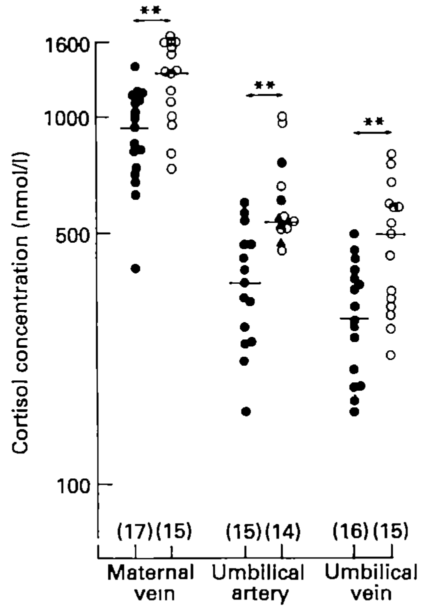

Fig. 1. Plasma cortisol (nmol/l). Bars indicate median values. ***$P<0{\cdot}001$ (Mann–Whitney two sample test). For clarity separate symbols are utilized for the three modes of vaginal deliveries for umbilical artery values only. (○) Vaginal delivery, (◉) breech; (▲) forceps; (●) caesarean section.

For glycerol, umbilical vein values were higher than artery levels in 11 out of 15 in the caesarean section group and 10 out of 12 in the vaginal delivery group. No linear relation was found between vein-artery glycerol and either maternal glycerol or umbilical artery noradrenaline concentration in either group.

Discussion

This study confirms that labour and vaginal delivery cause variable fetal sympatho-adrenal responses, as assessed by umbilical artery noradrenaline concentrations. The wide range of concentrations of noradrenaline reported in this study may reflect the variety of the mode of delivery included within this small subpopulation (Fig. 2). Previous studies have highlighted the magnitude of the sympatho-adrenal responses to vaginal breech delivery (Lagercrantz & Bistoletti 1977; Falconer & Lake 1982). In contrast, the sympatho-adrenal responses to delivery by elective caesarean section were less marked, although the concentration of plasma catecholamines in umbilical artery samples was high compared to that found in the human adult under stress, as exemplified by maternal venous blood levels during delivery. The difference in the magnitude of the fetal sympatho-adrenal response to delivery between the two groups in this study could not be explained wholly on the basis of acid-base disturbance as no significant differences were recorded in umbilical artery blood gases. However, those fetuses born with evidence of acid-base disturbance tended towards elevated catecholamine concentrations. The differences in the fetal 'stress response' to delivery between the two groups were further highlighted by significant elevations in artery blood cortisol concentration following labour and vaginal delivery. These differences, although less marked, confirmed those of Murphy & D'Aux (1972) who showed a three-fold rise in umbilical plasma cortisol between vaginal delivery and elective caesarean section. Parturition appeared to produce a greater cortisol surge in the mother with more pronounced sympatho-adrenal activity in the fetus.

Measurement of fetal concentrations of catecholamines, glycerol and glucose may be influenced by maternal levels of these substances. The relation between fetal sympatho-adrenal activity and metabolic responsiveness was influenced by maternal factors. There is little evidence to suggest that placental transport of catecholamines occurs in significant quantities; indeed, there is strong evidence to support placental uptake and oxidation of these compounds (Morgan *et al.* 1972; Castren & Saarikoski 1974; Chen *et al.* 1974). In contrast, blood glucose crosses the placenta by facilitated diffusion and fetal levels reflect maternal circulating concentrations (Widdas 1961). Umbilical artery glucose levels will be influenced indirectly by maternal venous blood glucose levels and directly by a balance between tissue uptake and endogenous glucose production (glycogenolysis and gluconeogenesis). In this study, between group differences in maternal blood glucose, although significant, were small. Surprisingly, in six cases (two caesarean section, four vaginal delivery) maternal venous blood glucose levels were higher than 5·5 mmol/l and in four of them these higher levels were reflected in high circulating insulin concentrations. In contrast, umbilical blood glucose concentrations were significantly higher in the vaginal delivery group; these values were similar to those reported by Hagnevik *et al.* (1984). These differences suggest that labour and vaginal delivery cause either diminished glucose uptake or an increase in

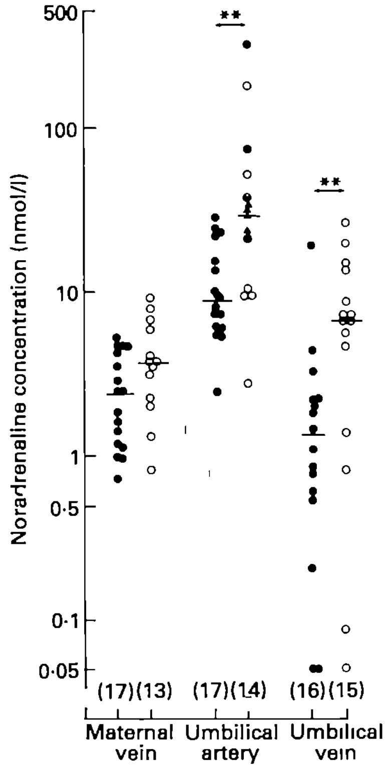

Fig. 2. Plasma noradrenaline concentration (nmol/l) Bars indicate median values. $^{**}P<0{\cdot}01$ (Mann–Whitney two sample test) For clarity separate symbols are utilized for the three modes of vaginal deliveries for umbilical artery values only. See Fig 1

endogenous glucose production in the fetus. Catecholamines may influence blood glucose concentration through β-mediated glycogenolysis or α-mediated inhibition of insulin secretion (Young & Landsberg 1977), but in this study high catecholamine levels were not associated with marked fetal hyperglycaemia.

Persson & Tunell (1971) found no consistent pattern in umbilical artery-vein glycerol patterns. In this study vein levels were higher than artery levels in all except six deliveries, suggesting either placental transport or mobilization of glycerol within the placenta. Maternal blood glycerol levels were significantly raised following vaginal delivery and this may partly explain the raised fetal levels in this group. High fetal plasma catecholamine levels were not consistently associated with an elevation in glycerol concentration

This study has demonstrated that the fetal

Table 3. Glucose, glycerol and insulin concentrations in maternal vein, umbilical artery and vein samples

	Maternal vein	Umbilical artery	Umbilical vein
Blood glucose (mmol/l)			
Vaginal deliveries	5·0*	4·80***	4·70**
	(3·60–6·70)	(3·20–5·50)	(3·30–6·20)
LSCS	4·50	3·00	3·60
	(3·80–6·30)	(2·10–6·30)	(3·20–4.70)
Blood glycerol (μmol/l)			
Vaginal deliveries	108**	60·5***	63·0***
	(47–173)	(12–113)	(18–199)
LSCS	77·5	19·0	26·0
	(47–145)	(4–45)	(12–181)
Plasma insulin (i.u./ml)			
Vaginal deliveries	13·0	9·0	6·0
	(4·0–35)	(2·0–14·0)	(2·0–22)
LSCS	11·0	9·5	11·5
	(4·0–35)	(7·0–21·0)	(3·0–26)

Results are median (ranges)
LSCS, Lower segment caesarean section.
Significance of difference between vaginal delivery and section (Mann–Whitney two sample test): $^*P<0·05$; $^{**}P<0·01$; $^{***}P<0·001$

metabolic responses to sympatho-adrenal activity at delivery were slight when compared to those recorded in the adult (Galbo 1975, 1976). Increases in blood glucose have been demonstrated in the chronically cannulated fetal sheep in response to an adrenaline infusion (Jones & Ritchie 1978). In the human newborn, marked lipolytic responses for thermoregulation (a rise in plasma glycerol to 270 ± 92 μmol/l) were reported within the first 2 hours of life (Persson & Tunell 1971; Swanstrom & Bratteby 1981). This evidence for sympatho-adrenal receptor responsiveness in fetal and early neonatal life suggests that sympatho-adrenal activity of labour is accompanied by an inhibition of metabolic responses.

Acid-base disturbances have been shown to reduce catecholamine mediated lipolysis in ani-

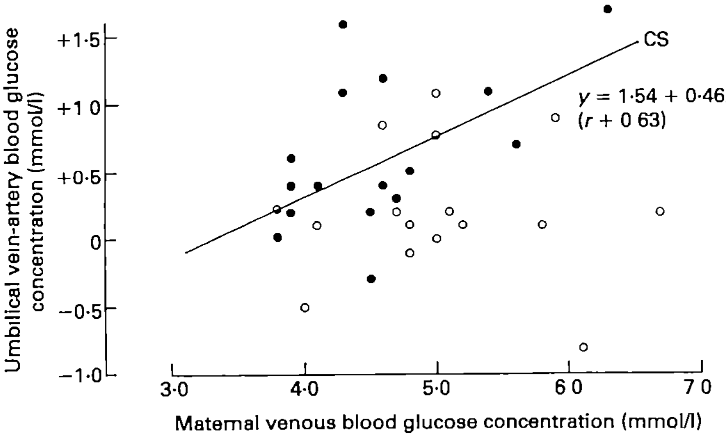

Fig. 3. Relation between maternal blood glucose concentration and umbilical vein-artery blood glucose concentration. A significant relation was demonstrable for the caesarean section (CS) group ($P<0·001$). No relation found for vaginal deliveries. (○) Vaginal delivery; (●) caesarean section (CS)

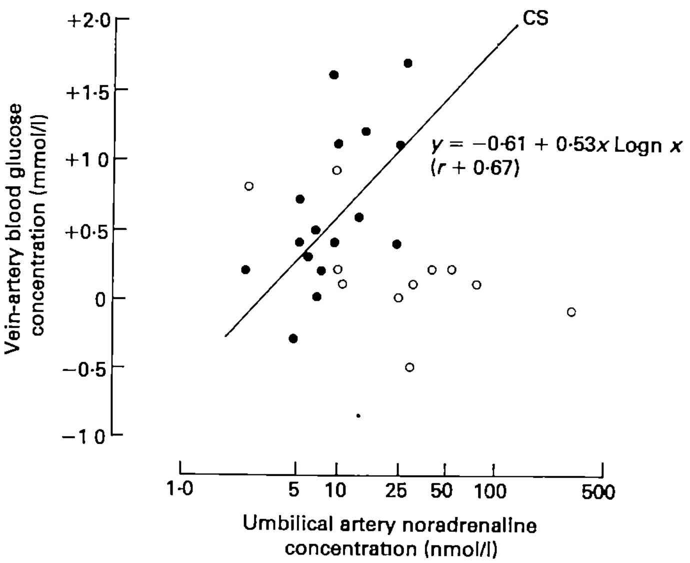

Fig. 4. Relation between umbilical artery noradrenaline concentration and umbilical vein-artery blood glucose concentration A significant relationship was demonstrable for the caesarean section (CS) group (P<0·001). No relationship found for vaginal deliveries. (○) Vaginal delivery; (●) caesarean section (CS).

mal models although in this study no between group differences were found for these variables. Under general anaesthesia, catecholamine induced lipolysis was significantly reduced during hypercapneic acidosis in Beagle dogs (Poyart & Nahas 1966). Hypoxia, which is frequently associated with high plasma catecholamine in the fetus, may reduce the lipolytic responses (Baum 1967). Such an inhibition of metabolic processes may be advantageous to the newborn infant in preserving adipose tissue for subsequent thermogenesis.

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The duration of lochia

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Summary. The duration of lochia and its association with a number of obstetric variables was studied in 236 women. Each woman completed a diary sheet describing the colour and duration of her lochia for up to 60 days post partum. The phases of lochia were divided according to the classical description; lochia rubra, serosa and alba. The median total duration of lochia was 33 days, lochia rubra 4 days and lochia serosa 22 days. Lochia persisted to 60 days in 13% of women. The duration of lochia was shorter in parous women and women with smaller babies.

Lochia is classically divided into three phases, lochia rubra, serosa and alba. The origins of this description remain obscure. The textbook description of the total duration of lochia varies from 18 days (Smellie 1752) up to 6 weeks (Dewhurst 1981). Whilst there have been a number of studies quantifying blood loss for the first few days post partum (Newton & Bradford 1961), we were unable to find a published study of the duration of lochia.

A prospective study was performed to determine the length of each phase of lochia and how these may be influenced by a number of obstetric variables.

Subjects and methods

All women who were delivered at St Thomas' Hospital over a 10-week period were invited to participate in the study. A total of 617 women was interviewed by one of us within 48 h of delivery of a live infant (including eight sets of twins) and agreed to complete a diary sheet for up to 60 days post partum.

Each day women were asked to record one of three categories that best described the colour of their lochia. The choices were labelled red (lochia rubra), brown-pink (lochia serosa) and yellow-white (lochia alba). A fourth choice, no loss, was recorded once vaginal loss had ceased or a normal pre-pregnant discharge had returned. Also recorded was the method of infant feeding, the type of contraception, the date of resumption of intercourse and the return of normal menstruation. Full instructions and a pre-paid addressed envelope were supplied with each diary sheet

Diary sheets were returned when either no loss had been recorded for 7 consecutive days or the diary sheet had been kept for 60 days. A pilot study, in which return was allowed only at 60 days, had indicated that this time limit was a reasonable compromise between patient compliance and cessation of lochia, and no woman was found to restart lochia after 7 days of no loss except to record a menstrual period At 30 days after delivery a reminder was sent to all women who had not yet returned their diary sheet. Data from the completed diary sheets was matched with the patients data obtained from the obstetric case notes (Table 1). In most cases the colour changed sequentially from red to pink to yellow; where there was fluctuation between

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Table 1. Obstetric variables examined for a relation with the duration of lochia

Maternal age	Induction of labour
Duration of normal menses	Mode of delivery
Ethnic origin	Placental weight
Smoking habit	Birthweight
Parity	Infant sex
Previous uterine scar	Method of infant feeding
Maternal booking weight	Oral contraception postpartum
Gestational age at delivery	Resumption of sexual intercourse

colours (63 returns), the predominant colour was recorded. Spoilt returns were defined as those in which fluctuations were uninterpretable (6), or where data was incomplete or incorrectly recorded (19). these returns were not included in the analysis.

The data were analysed by computer using the Minitab statistical package (Ryan *et al.* 1981). Median values for duration are quoted because of the skew nature of the distribution. Variability is indicated by the interquartile range (25th–75th centiles). Duration of lochia is compared between sub-groups of patients using the non-parametric Kruskal–Wallis test.

Results

The overall return rate was 261 (42%) of which 25 returns were spoilt, leaving 236 for analysis. The groups of 'returns' and 'non-returns' were compared for age, parity and ethnic origin and though broadly similar, there was a trend in that those returning tended to be older, white and of lower parity, suggesting that they were of higher social class (Table 2).

The duration of lochia in the complete study group is seen in Fig. 1 which shows a survival plot of lochia rubra, serosa and total duration of lochia. Because 87 patients (36%) did not experience lochia alba, their vaginal loss ceasing with lochia serosa, the curve for total duration of lochia includes both these 87 patients and those with lochia alba. The median duration of lochia rubra was 4 days (interquartile range 2–6 days), lochia serosa 22 days (16–35) and total duration of lochia 33 days (23–48). At 60 days 4% of patients still had lochia serosa and 9% lochia alba Periods were recorded by 50 patients before the return of their diary sheet. No woman recorded the fitting of an intrauterine contraceptive device before the cessation of lochia.

Each of the obstetric variables listed in Table 1 was individually examined for an effect on the duration of lochia. Other variables, which may have been of interest such as twin pregnancy and retained placenta at delivery, produced insufficient numbers for analysis. The median total duration for the cessation of lochia was significantly influenced by two variables: increasing parity (Table 3) was associated with a decreasing median duration of lochia; increasing birthweight (Table 4) was associated with an increasing median duration of lochia. No other obstetric variables showed a significant ($P<0\cdot05$) relation with duration of lochia.

Discussion

These results confirm a clinical impression that lochia persists for longer than is generally appreciated. Overall, 15% still had a pink loss (lochia serosa) at 42 days (time of the traditional postnatal examination) and 4% at 60 days. Malvern & Campbell (1973) examined 117 women with clinically significant vaginal bleeding up to 6 weeks post partum and though more than one third underwent curettage of the uterus, based on clinical and ultrasonic findings, only 10 (8·5%) were found to have histological evidence of retained products of conception. Many of the remaining 91·5% may have been losing normal lochia. Only two of our study patients had a

Table 2. Numbers of returns and non-returns analysed according to age, parity and ethnic group

	Non-return	Return*
Age (years)		
16–19	48 (13)	25 (10)
20–29	230 (65)	141 (54)
30–39	74 (21)	90 (34)
40+	4 (1)	5 (2)
White European	232 (65)	190 (73)
Other	124 (35)	71 (27)
Parity		
0	157 (44)	135 (52)
1	118 (33)	82 (31)
≥2	81 (23)	44 (17)

Percentages are in parentheses.

* Includes 25 spoilt returns.

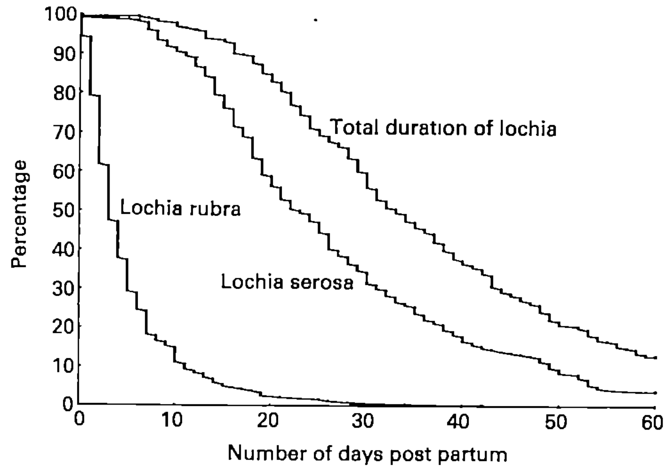

Fig. 1. Survival plot showing percentage of women ($n = 236$) who continue to experience lochia, according to phase. Lochia alba is included in the curve for total duration of lochia (see text)

curettage and both were performed within 1 week of delivery.

Williams (1931) in his study of post-partum endometrial regeneration, later confirmed by Sharman (1953), found that while the non-placental endometrium has completed regeneration by the end of the third week, that of the placental site was not complete until the sixth or seventh week. This process was achieved by exfoliation of cells rather than re-absorption in situ. Our finding of a median duration of lochia of more than 4 weeks suggests that exfoliation of cells from the placental bed maybe a significant contributory factor in lochial loss beyond 3 weeks. Any factor influencing duration of lochial flow may act via an effect on rate of endometrial regeneration.

Table 3. Relation between parity and median total duration of lochia

Parity*	No. of patients	Total duration of lochia (days) Median (25th–75th centile)
0	124	38 (26–50)
1	76	30 (22–43)
≥2	36	27 (19–36)

* Includes all pregnancies of >28 weeks.
Significance of difference $P<0{\cdot}002$

Table 4. Relation between infant birthweight and median total duration of lochia

Birthweight (kg)	No. of patients	Total duration of lochia (days) Median (25th–75th centile)
<3	52	29 (20–38)
3–3·9	145	35 (23–49)
≥4	39	41 (28–56)

Significance of difference $P<0{\cdot}005$.

In this regard, the finding of a significant relation between duration of lochia and increasing birthweight ($P<0{\cdot}005$) but not placental weight ($P>0{\cdot}05$) is interesting since Thomson *et al.* (1969) have demonstrated that birthweight and placental weight are well correlated. It is possible, therefore, that the rate of endometrial regeneration is in some way related to the weight of the baby, perhaps by the degree of uterine distension prior to delivery, and is not simply a function of the size of the placental bed.

Having demonstrated an association between the duration of lochia and increasing birthweight, an increase in duration of lochia with parity might have been expected since increasing birthweight and parity are related (Thomson *et al.* 1968). However, the opposite proved to be the case. A possible explanation for this could be that the small increase in average birthweight noted between primigravidae and multigravidae (100 g in our study) was outweighed by the more efficient involution of the parous uterus. The observation of an inverse relation between parity and duration of lochia is not new. Hippocrates is reported to have stated that 'those women who are having their first child suffer most at childbirth and during purgation and those who have had fewer children suffer more than those who have had more' (Ellinger 1952). Sadly we were unable to confirm the Hippocratic opinion that 'lochial purgation lasts generally 42 days when the child is a female . . . when the child is a male purgation lasts 35 days.'

Hormonal influences on the puerperal uterus are poorly understood. Breast-feeding, which produces ovarian suppression with raised prolactin levels (Howie *et al.* 1982), might have been expected to influence the duration of lochia, but no significant association was found. In addition, neither the progesterone-only pill (started about the 10th day) nor the combined oral contraceptive (started at any time during the study) had any significant effect.

A low return rate (42%) in this type of study might be expected. It is the characteristics of the target population rather than the experimental design that has most bearing on return rates (Kaplan & Cole 1970) and puerperal women once home have many responsibilities. Bias may be introduced in a study such as this in two ways. Firstly, the responders may constitute an unrepresentative sample of the total population, and the possible influence of social class has already been mentioned. Secondly, variation in the duration of lochia itself may have affected the response rate, but because women were permitted to return their diary sheets after the cessation of lochia, those who had an extremely short duration of lochia were as likely to remember to return their forms as women still bleeding at 60 days.

In order to simplify both the response and analysis, only three categories of lochia were permitted. To a certain extent, this distinction is artificial as the colour of lochia is, in all probability, a continuous spectrum. Indeed, more than one third of women in this study did not experience a lochia alba phase.

This study demonstrates that prolonged vaginal loss in the puerperium, which can be a difficult clinical problem, is neither unusual nor necessarily abnormal. It is suggested that the traditional teaching on the duration of lochia needs reappraisal.

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Mast cells in the tubal wall in women using an intrauterine contraceptive device

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Summary. The number of mast cells in the tubal wall of 33 healthy non-pregnant women, 17 of whom had an intrauterine contraceptive device (IUCD), was investigated. Light microscopy showed that both the muscularis externa and the lamina propria of the tubal wall contained more mast cells in the 17 IUCD users than in the 16 non-users (control group). In both patient groups the mast cell concentration was higher in the muscularis externa than in the lamina propria. Most mast cells of the muscularis externa were more closely related to smooth muscle cells than to blood vessels. The increased number of mast cells in IUCD users may be a factor in the pathogenesis of pelvic inflammatory disease and the ectopic pregnancies that occur in IUCD users.

Ectopic pregnancies occur more frequently in women using an intrauterine contraceptive device (IUCD) (Tatum 1977; Savolainen & Saksela 1978). Pelvic inflammatory disease (PID) also occurs more often in IUCD users than in non-users (Westrøm *et al.* 1976; Beerthuizen *et al.* 1982). It seems reasonable to relate the increased prevalence of tubal pregnancies to such inflammatory changes.

In a previous paper we described a pronounced reduction of ciliated cells in the endosalpinx of IUCD users (Wollen *et al* 1984), and in this paper we report an increased number of mast cells in the tubal wall of IUCD users. Mast cells are known to contain potent biological mediators and these may be responsible for local inflammatory reactions (Wasserman 1979). Consequently mast cells in the tubal wall may play a central role in the unwanted side effects associated with the IUCD.

Subjects and methods

An 1-cm segment of the isthmic portion of the oviduct was removed during laparotomy or laparoscopy from 33 healthy non-pregnant women undergoing sterilization, 17 of them had used an IUCD for >6 months (study group) and the other 16 (control group) had not used an IUCD nor hormonal contraception. Fifteen of the IUCDs incorporated copper wire. The two groups were similar for age and parity (Table 1). Three of the IUCD users had previously suffered from salpingitis.

Immediately after removal, the biopsies were fixed in 1% formaldehyde, 2·5% glutaraldehyde, 0·06 M sodium cacodylate buffer at pH 7·4, and approximately 60% Ringer's solution. Tubal cross sections, about 1 mm thick, were cut after 1–3 days in the fixative at 4°C and rinsed overnight in a similar solution lacking aldehydes. Later the tissue blocks were postfixed in 1% OsO_4 in the rinsing solution for 3 h, washed in two changes of distilled water, dehydrated in ascending concentrations of acetone and embedded in Agar epoxy plastic.

For light microscopy, 1 µm cross-sections of

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Table 1. Characteristics of the patient groups

	IUCD-users (n = 17)			Controls (no IUCD) (n = 16)			Significance of difference Student's t-test
	Mean	SD	Range	Mean	SD	Range	$2P$
Age (years)	37·3	3·6	31–44	37·8	4·2	29–43	0·7
Parity	2·4	0·6	2–4	2·8	0·8	2–4	0·11
Gravidity	2·5	0·7	2–4	3·1	1·1	2–5	0·08

the tubal wall were stained with 1% toluidine blue in 1% sodium tetraborate. Mast cells were identified, counted, and their location relative to other tissue components noted at a magnification of × 560. The sections were then photographed at low magnification, and the total area of tubal epithelium, submucous connective tissue and muscular wall measured on a Kontron MOP AMO3 morphometrical analyser.

For transmission electron microscopy, ultrathin sections were cut on a LKB Ultrotome V ultramicrotome, mounted on formvar and carbon coated copper grids, stained with 1% uranyl acetate in distilled water and lead citrate (Reynolds 1963) and examined in a JEOL 100 CX or a Philips EM 300 transmission electron microscope.

For statistical analysis Wilcoxon's 2-sample test and Student's t-test were used.

Results

The cross-sectioned tubal lumen in 18 biopsies (seven with and 11 without an IUCD) was small with three to five epithelial folds and was representative of the isthmic portion. However, in spite of the fact that all biopsies were taken from the isthmic portion of the oviduct, 14 biopsies (10 with and four without an IUCD) contained a large lumen with highly elaborate epithelial folds, as in the ampullary region.

With the light microscope the mast cells were seen to be elongated cells with intensely stained basophilic granules, less than 1 µm wide, filling the entire cytoplasm. Some cells appeared to be partially 'degranulated' and basophilic granules were scattered throughout the surrounding extracellular space (Fig. 1). As the metachromatic reaction does not work well on semithin epoxy sections, we used the electron microscope for definitive identification of these cells. No attempt was made by light microscopy to distinguish between different types of mast cells.

With the electron microscope the mast cells were seen to possess several leaf-like cytoplasmic projections (80–100 nm in width and 1–3 µm in length) into the surrounding extracellular matrix. The cytoplasm was packed with membrane bounded bodies 0·4–0·8 µm in diameter with electron density varying from almost black to light granular grey (Figs 2 and 3). Beyond these granules some small mitochondria, and a dense cytoplasmic ground substance dominated by numerous free ribosomes, and some filaments were the only structures seen (Fig. 3b).

Some of the electron dense cytoplasmic bodies contained tiny cylindrical inclusions with filaments disposed in circular or spiral-shaped parallel patterns (Fig. 3a). These scrolls are specific for human mast cells (Caulfield *et al.* 1980). In most granules the dense matrix filled the membrane vesicle completely, whereas others appeared to contain a partly dissolved matrix (Fig. 2b).

Light microscopy of one semithin section from each of the 33 biopsies identified a total of 700 mast cells. Aggregates of mast granules, lacking a well-defined cellular appearance (like those marked Mg in Fig. 1a and 1b) were not included in this survey. The mast cells were found with variable frequency in both the lamina propria and the muscular part of the wall, but never in the tubal epithelium. All biopsies contained mast cells in the muscularis, but five sections from the IUCD users and six from the non-users lacked such cells in the lamina propria.

The average concentration of mast cells was higher in the muscularis than in the lamina propria in both groups and higher in both layers in the IUCD users than in the control group. In the muscularis the difference between the two groups was statistically significant ($P<0{\cdot}01$)

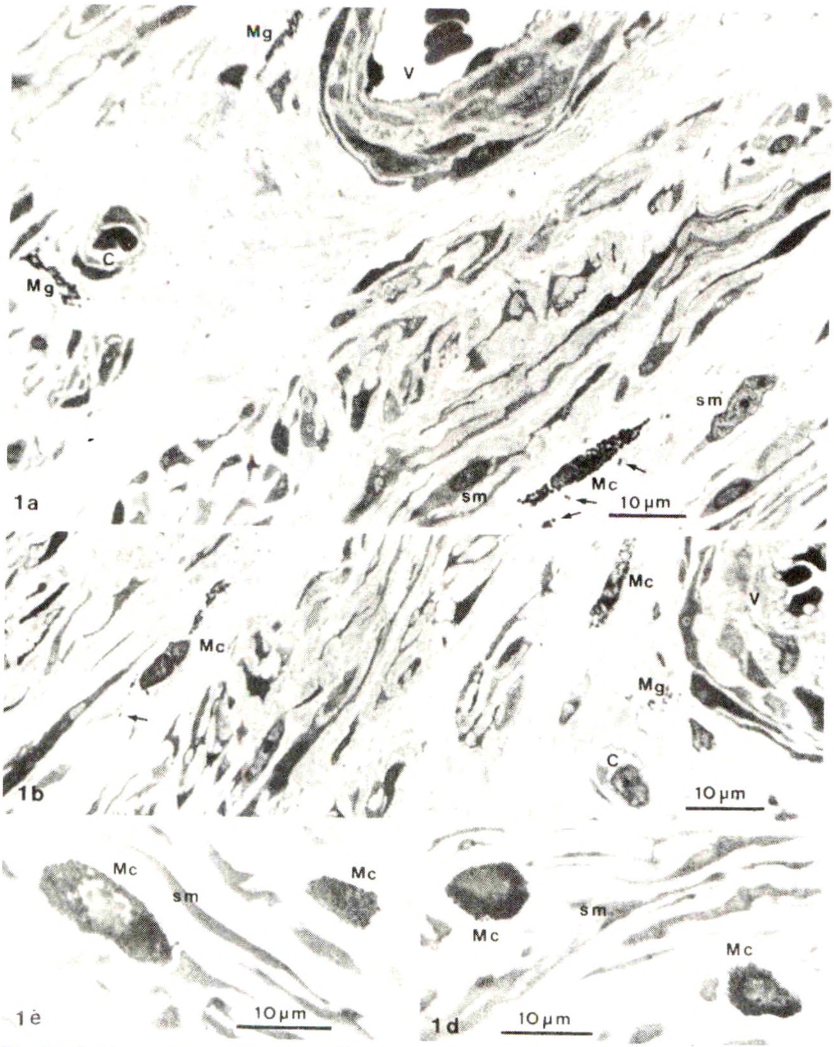

Fig. 1a–d. Light micrographs of toluidine blue stained semithin sections from the muscular part of the tubal wall of an IUCD user. Mast cells (*Mc*) and mast cell granules (*Mg*) are located next to capillaries (*c*), smaller veins (*v*) and between smooth muscle cells (*sm*). Some scattered mast granules are probably derived from neighbouring mast cells by degranulation. (Arrows).

(Table 2). In the control group 51% of the mast cells appeared degranulated to a variable degree. In the IUCD users degranulation was less prominent, involving only 38% of the mast cells. However, because of the higher total number of mast cells in this group, 1·7 times as many mast cells were degranulated compared with the control group.

No significant differences were found in the density of mast cells per mm^2 sectioned tissue between biopsies with an isthmic or ampullar appearance in either group of subjects (Table 3).

When the biopsies were grouped according to the phase of the menstrual cycle, secretory phase biopsies appeared to contain slightly more mast cells than were seen in proliferative phase biopsies. The difference was statistically significant only in the control group. The lack of significance in the IUCD group could perhaps be due to the limited number of biopsies examined.

Within the muscular part of the tubal wall most mast cells were closer than one cell width from the nearest smooth muscle cell. In the IUCD users the mean distance was 2·4 (SD 3·2) µm ($n = 415$), and in the control group 4 (SD 5) µm ($n = 188$). The difference was statistically

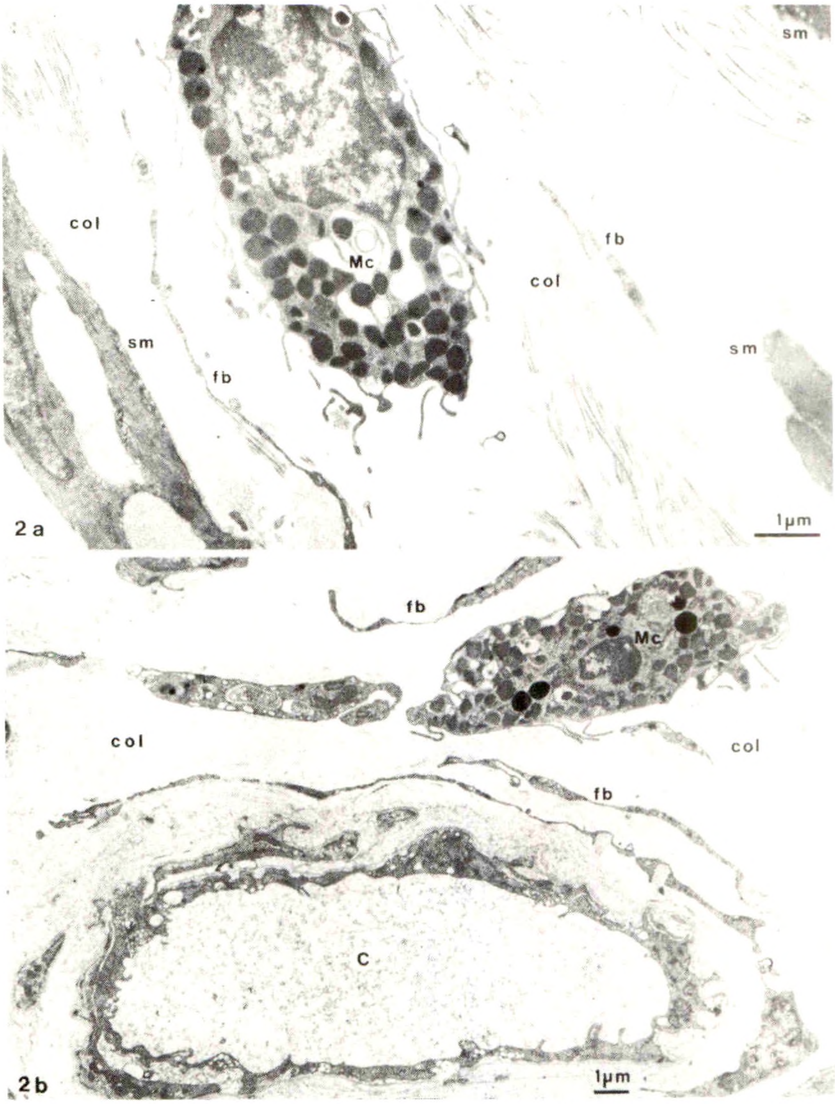

Fig. 2. Transmission electron micrographs of (a) a mast cell (*Mc*) completely surrounded by smooth muscle cells (*sm*) and fibroblast processes (*fb*) in a collagenous matrix (*col*) and (b) a mast cell (*Mc*) next to a capillary (*c*) and fibroblast processes (*fb*), also in a collagenous matrix (*col*). Note the variable density of the mast granules in (b) and the numerous cytoplasmic processes of both mast cells.

significant ($P<0{\cdot}025$). Only about half of these mast cells were within five cell widths from indentifiable small blood vessels. Even selecting only such cells showed that their mean distance to the external border of the vessel-wall was about three times that to the smooth muscle cells, 10·4 (SD 7·2) μm ($n = 174$) in IUCD users and 10·4 (SD 7·2) μm ($n = 104$) in the control group. The difference was statistically significant in both groups ($P<0{\cdot}025$).

In the lamina propria the mast cells appeared to be slightly closer to blood vessels. In IUCD users the mean distance was 6·4 (SD 4) μm ($n = 50$) and in the control group 7·2 (SD 5.6) μm ($n = 43$). This difference was not statistically significant (Table 4).

The relation of the mast cells to other tissue components within the muscular part of the tubal wall of IUCD users was also examined by transmission electron microscopy. Our preliminary results indicate that 11 of 18 mast cells were situated <5 μm from autonomic nerve

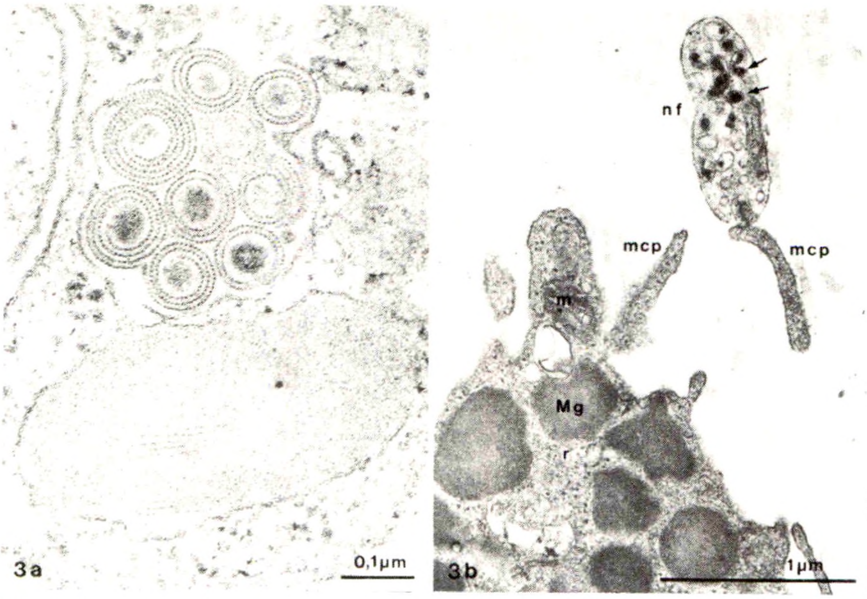

Fig. 3. (a) Transmission electron microscopic detail of two mast granules with scroll-like inclusions. (b) Transmission electron micrograph of a naked nerve fibre ending (*nf*) in close proximity to a mast cell and its processes (*mcp*). The dense core synaptic vesicles (*arrows*) indicate that the nerve terminal contain monoamines. Mg, Mast cell granule; m, mitochondrion; r, ribosomes.

Table 2. Number of mast cells per mm^2 sectioned area of tubal wall

	IUCD users ($n = 17$) Median (range)	Control group ($n = 16$) Median (range)	Significance of difference Wilcoxon's two sample test
Lamina propria	7·9 (33·3)	3·8 (34·0)	NS
Muscularis externa	22·8 (52·5)	10·4 (59·6)	$P<0{\cdot}01$
Lamina propria plus muscularis externa	14·3 (49·9)	8·0 (44·6)	$P<0{\cdot}01$

Table 3. Number of mast cells per mm^2 sectioned area of tubal wall in the different parts of the fallopian tube

Group	No. of biopsies	Lamina propria Median (range)	Muscularis Median (range)	Lamina propria plus muscularis Median (range)
IUCD users ($n=17$)				
Isthmus	7	17·0 (33·3)	23·3 (52·5)	20·4 (49·9)
Ampulla	10	6·7 (33.2)	22.3 (43·0)	14·2 (36·5)
Control group ($n=16$)				
Isthmus	11	0·0 (34·0)	7·6 (59·6)	6·0 (44·6)
Ampulla	4	8·7 (12·1)	16·9 (14·8)	11·6 (6·1)
Unknown	1	0·0	5·1	4·6

There were no significant differences in the density of mast cells between isthmus and ampulla in the different parts of the fallopian tubes in either groups (Wilcoxon's two samples test)

Table 4. Distance from mast cells to nearest smooth muscle cell and blood vessel in different parts of the tubal wall

	Muscularis externa				Lamina propria		
Patient group	Distance to muscle cell (µm) (D1)	No. of mast cells	Distance to capillary (µm) (D2)	No of mast cells	Distance to capillary (µm) (D3)	No of mast cells	Significance of difference D1 *vs* D2
IUCD users ($n = 17$)	2·4 (3·2)	415	10·4 (7·2)	174	6·4 (4·0)	50	$P<0{\cdot}025$
Control group ($n = 16$)	4·0 (5·0)	188	10·4 (7·2)	104	7·2 (5·6)	43	$P<0{\cdot}025$

Results are means (SD) values

fibres (Fig. 3b). Two of the 18 mast cells could also be characterized as being perivascular. One of these was also perineural (Fig. 2b) The rest of the mast cells was entirely surrounded by smooth muscle cells and fibroblasts (Fig. 2a).

Discussion

Although the metachromatic staining reaction was not tested for the mast cells in this study, electron microscopy of at least 50 cells with strongly basophilic granules showed that they all contained typical mast granules of either the scroll, crystalline, particulate or combined type (Kawanami *et al.* 1979). Their origin as macrophages or basophile leukocytes could therefore be ruled out.

The increased number of mast cells found in the tubal wall of IUCD users as compared to non-users has to our knowledge never been reported before. However, this observation agrees well with the previously reported abundance of mast cells in the uterine wall of women using an IUCD (Sheppard & Bonnar 1979) and of hamsters with an implanted IUCD (Moore *et al.* 1979). Increased numbers of mast cells have also been reported from uterine smears of women using an IUCD (Tursi *et al.* 1984).

In our study the mast cells seemed to be most abundant in biopsies taken during the secretory and menstrual phases in both IUCD users and control subjects. This is in agreement with the cyclic variation of mast cells found by Iversen (1960) in the cervix uteri of women not using an IUCD. Foley *et al.* (1978) have proposed that the heparin content of these mast cells may contribute to the pathogenesis of excessive bleeding and dysmenorrhoea, both conditions which are more often seen among IUCD-users.

The density of mast cells in the tubal wall in our study (Tables 2 and 3) is in the lower range of those reported in other tissues such as skin, colon and bronchus (Eady 1979; Thompson & Buchmann 1979; Connell 1971). Our lower densities, however, may reflect the smaller thickness of our sections (1 µm) compared with 5–10 µm sections studied by these authors, rather than to any real difference in mast cell density.

The association between increased mast cell density and chronic inflammation has been known since the work of Ehrlich (1879). The role of tubal mast cells in the initiation, maintenance and repair of inflammatory reactions is not understood and is likely to be very complex. Mast cell activation can be caused by several agents, including IgE and neurotensin, and such activation results in the liberation of a variety of biologically active mediators including vasoactive, chemotactic and proteolytic substances (Wasserman 1979). Mast cell mediators may also minimize rather than enhance inflammatory processes, which could be the case in IUCD users who have increased numbers of mast cell without signs of inflammation (Tursi *et al.* 1984).

Mast cells have been shown to take part in axon reflex vasodilatation in the skin (Kiernan 1975) and to degranulate upon electrical stimulation of the associated nerves in the presence of an α-blocking agent in the human omental veins (Thureson-Klein & Stjärne 1979).

Mast cells have important functions to perform in normal tissue (Padawer 1979). We are of the opinion that the mast cells in the fallopian tubes relate to muscular dynamics rather than to vascular permeability.

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Absorption of menstrual discharge by tampons inserted during menstruation: quantitative assessment of blood and total fluid content

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Summary. The simultaneous absorption of genital secretions and blood was assessed in 61 intravaginal tampons from eight young, healthy, nulliparous volunteers during menstruation. The tampons were self-inserted over the first 3 days of menstruation according to the habit of each subject. Wide variations in the amount of blood and fluid absorbed were noted within and between subjects. The mean amount of genital secretion absorbed was 0·31 g/h and that of menstrual blood was 0·76 g/h. The average tampon absorbed 65% blood and 35% genital secretion.

After many years of inactivity, renewed interest in catamenial products and their possible effects on the vagina and the perineal area was stimulated by the occurrence of toxic shock syndrome in menstruating women wearing tampons (Institute of Medicine 1982), and several articles on this subject were published in *Ann Intern Med* (1982) **96**, (6 Part 2). Although there have been many observations on the loss of menstrual blood (Barer & Fowler 1936; Stevenson *et al.* 1945; Hallberg & Nilsson 1964*a,b*; Rybo 1966; Shaw 1973; Shaw *et al.* 1972) only one recently published study has attempted to quantify the amount of blood absorbed by an intravaginal tampon during menstruation to the total menstrual discharge (Fraser *et al.* 1985). Such information is of value as it is claimed that tampons may damage the vaginal epithelium even during menstruation (Friedrich 1981) and it allows quantification of the errors involved in methods that monitor menstrual blood loss by directly weighing the sanitary protection before and after use (Pendergrass *et al.* 1984). The present investigation was instigated to quantify the relation between the amount of blood absorbed by an intravaginal tampon to the total amount of menstrual discharge during menstruation in healthy young volunteers and is part of a wider study on human vaginal physiology (Wagner & Levin 1978*a,b*, 1980; Wagner 1979; Levin 1980; Wagner & Ottesen 1982; Wagner *et al.* 1984). In the context of the study, genital secretion is defined as the mixture of fluid and solids present in the vaginal lumen apart from blood. This secretion is heterogeneous consisting mainly of uterine, cervical and vaginal secretions, exfoliated cells and bacteria with possible minor contributions from the fallopian tubes, glands of Skene and Bartholin and contamination by urine (Wagner & Levin 1978*a*, 1980).

Subjects and methods

The study was approved by the local ethics committee. The Helsinki Declaration was followed, and written, informed consent was obtained

The experiments were conducted with volunteer student nurses who were paid a nominal fee for participating. They were aged between 22 and 24 years, were healthy and nulliparous, had

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no previous gynaecological diseases and were not using steroid contraception.

The tampons used were Tampax (regular; Tambrands Ltd.) purchased commercially from random sources. Each tampon was removed from its cardboard inserter and placed in a serially numbered, plastic phial fitted with a snap air-tight lid. The whole was weighed and the weight recorded. A record card with the tampon number upon which times of insertion and removal could be written was given to all the subjects. They were told to maintain their normal tampon usage/procedures and to change them according to their own personal habit. On removal of the used tampon they were asked to return it to its numbered container, then seal it immediately with its lid. The insertion and removal times were recorded by the subject on the sheet. The used tampons were brought to the laboratory the next day and weighed immediately. The current tampon worn by the subject was then removed and weighed in its phial. All tampons were subsequently removed from their phials, cut quickly into small pieces into individual numbered 200-ml beakers with surgical scissors and the pieces were extracted with 20 ml of distilled water. The water was forced into and from the cut tampon by using a plastic multiperforated disc plunger with a diameter (4·5 cm) that just fitted the beakers. Approximately 10–15 strokes of the plunger were used to facilitate extraction of the blood from the tampon. As much fluid as possible was then expressed from the tampon into a graduated cylinder by strong manual pressure and the volume noted. This varied from 8 to 15 ml and was obviously dependent on the amount of blood initially absorbed by the tampon. The expressed volume was then centrifuged for 10 min to spin down cellular debris. After centrifugation a sample of the supernatant was taken for determination of the haematin content by pipetting 0·5 ml into 4·5 ml of 5% NaOH (Shaw *et al.* 1972; Hallberg & Nilsson 1964*b*). The tampon residues containing trapped blood and the remaining extracting fluid were then added to 200 ml of 5% NaOH in a 500 ml beaker. Vigorous stirring for a few minutes ensured that the blood and fluid in the tampon was mixed with the alkali. The beaker was then covered with plastic film, held in place with a rubber band, to prevent evaporation. After standing for 48 h at room temperature the alkali was decanted off, spun down and its optical density measured at 545 nm together with the alkali haematin obtained from the initial water extract of the tampon. The amount of blood on the tampon in ml was calculated by the method of Shaw *et al.* (1972), using a sample of the subject's venous blood (obtained mostly at the onset of menstruation) to prepare the alkaline haematin standard. The concentration of haematin in the original extract of the tampon multiplied by the volume of the fluid collected gave the amount initially extracted from the tampon, while the concentration in the 200 ml of final extract multiplied by the total fluid volume present gave the amount of residual haematin left in the tampon that could not be squeezed out by the plunger. Addition of these two estimates allowed the total amount of haematin (and thus blood) to be calculated. For calculation purposes it was assumed that the specific density of blood was equal to that of water (i.e. 1 ml blood=1 g). The total wet weight of the genital material collected on the tampons was corrected for its dry weight content. The dry weight/wet weight ratios of material collected on 10 tampons during the menses of three subjects (obtained by heating the wet, soiled, weighed tampons to dryness and re-weighing) ranged from 79 to 92% with a mean of approximately 85%. This compares reasonably with the 88% reported by Bussing (1957). The mean percentage wet weight was used to correct the observed wet weight of the tampon contents from all the subjects into a 'fluid-only wet weight'. By subtracting the amount of blood found from this corrected 'fluid-only wet weight' for each individual tampon, an estimate of the amount of genital fluid other than the menstrual blood *per se* could be assessed. In six tampons (approximately 10%) with large amounts of blood and small amounts of genital secretion the various applied corrections led to errors so that the estimated amount of blood on the tampon was slightly greater than its total weight leading to apparent negative values for genital fluid secretion rate. These errors occurred because an overall mean value for the dry/wet weight ratios had to be applied to all tampons despite obvious variations that exist in specific cases. The negative values were regarded as representing zero absorption of genital fluid.

The haemoglobin content of the subject's blood was estimated by the cyanmethaemoglobin method (Merckotest kit). The range of normal haemoglobin values for females with this kit was 12–16 g/10 dl. All the subjects were found to be within this range (Table 1).

Table 1. Details of contraception used and haemoglobin concentration in eight subjects.

Subject	Contraception	Hb (g/10 dl)
1	Sheath	13·7
2	Diaphragm	14·6
3	Sheath	13 2
4	Sheath	13·3
5	Sheath	12·8
6	Cu-IUCD	12·4
7	Cu-IUCD	13·5
8	Cu-IUCD	13·2

Cu-IUCD, Intrauterine contraceptive device with copper wire.

Results

The relation of the amount of blood to the amount of genital fluid collected on consecutive tampons inserted serially by eight healthy subjects during the first few days of menstruation was assessed. Table 2 lists the results for the serial tampons used by each of the eight women; the duration of insertion, the corrected amount of genital secretion absorbed per hour, the amount of blood absorbed per hour and the percentages of blood and genital secretion on each tampon. The data show a wide range of values for the amount of blood present and the amount of genital secretion absorbed both between and within subjects. There was no evidence that the three women using the Cu-IUCD had any greater blood loss than those using the sheath or diaphragm methods of contraception as their mean blood loss, standard deviations and range of loss were well within the values shown by the other subjects.

The percentage of blood absorbed by tampons varied from 10% to the maximum 100%, a range actually observed for the tampons of subject no 2. The few negative values obtained for the amount of genital secretion collected per hour in subjects 2, 4, 5 and 6 are due to the technique used to correct the secretion weight to a 'secretion fluid-only-weight' as detailed in the methods section. They have been regarded as zero secretion collections in the calculations of measurements, etc.

Because the tampons were inserted serially in each subject, it was possible that those inserted earlier during menstruation would absorb more genital secretions than those inserted later. However, inspection of the data in Table 2 reveals no clear pattern and this hypothesis is unsupported.

A tabulated summary of the means, medians and the grand means of the means and medians for the hourly amounts of genital secretion and of blood absorbed by the tampons are collected in Table 3 together with the mean and medians for the percentages of blood and secretion in the groups of tampons for each individual's menses. In most cases there is a good agreement between the calculated mean and median suggesting that the data were distributed normally. The grand mean (for all the data) indicates that approximately 65% of the material collected on a tampon during menstruation is blood while 35% is genital secretion. The grand mean for the amount of genital secretion absorbed per hour on the 61 tampons from 8 subjects was 0·31 g/h. This is remarkably similar to the mean amount of genital fluid collected from the vagina (0·33 SD 0·05 g/h) during the intermenstrual period when a tampon was collecting secretion for a few hours daily, as described in the study by Wagner & Levin (1980).

Discussion

It is obvious from our results with just eight subjects that the percentage of genital secretion absorbed, in relation to blood absorbed by tampons during menstruation, varies over a very wide range of values from 1 to 92%. The mean value for the relative amount of secretion absorbed on a tampon during the first 3 days of menstruation approximates to 35% of the wet weight. This proportion is in close agreement with the brief statement of Hallberg & Nillson (1964*a*) that the total menstrual volume is some 60% greater than the blood volume, giving a genital secretion volume some 37% of the menstrual volume.

Our data also clearly show no particular pattern of the amount of secretion in relation to the serial, temporal sequence of tampon usage. There is no evidence that the early inserted tampons absorbed more genital fluid than later ones. The relation between the absorption of blood and that of genital secretion is complex and as our data show, each tampon insertion must be regarded as a unique combination of dynamic events. The balance between the amounts of various genital secretions formed, the blood loss and the duration of insertion are independent variables that change for each occasion.

Table 2. Amounts and percentages of genital fluid secretion and blood absorbed on tampons inserted serially in eight subjects

Serial tampon numbers	Duration of insertion (h)	Fluid secretion (g/h)	Blood (g/h)	Blood (%)	Fluid secretion (%)
Subject 1					
1	3·5	0·33	0·26	44	56
2	3	0·79	0·59	43	57
3	6	0·31	1·08	78	22
4	3·5	0·47	1·00	68	32
5	2·5	0·23	0·72	76	24
6	3·5	0·55	0·60	52	48
Mean	—	0·45	0·71	60	40
Subject 2					
1	2·5	0·23	0·76	77	23
2	3	1·81	0·20	10	90
3	1	0·13	0·80	86	14
4	11·5	0·13	0·40	76	24
5	2	0	2·9	100	0
6	2	0	3·5	100	0
7	1	0·18	1·6	90	10
Mean	—	0·35	1·45	77	23
Subject 3					
1	3	0·44	0·30	41	59
2	3·25	0·29	0·15	34	66
3	4	0·51	0·18	26	74
4	7·5	0·24	0·23	49	51
5	4	0·71	1·25	64	36
6	2·25	0·53	0·62	54	46
7	6·75	0·12	0·33	73	27
8	9·75	0·12	0·08	40	60
9	1·5	1·39	0·53	28	72
Mean	—	0·48	0·41	45	55
Subject 4					
1	4·5	0·20	1·24	86	14
2	9	0·15	0·16	52	48
3	3·75	0·12	1·07	90	10
4	1·75	0·02	2·69	99	1
5	2·75	0·10	0·65	87	13
6	3	0·14	1·67	92	8
7	4	0	1·23	100	0
8	2·25	0·47	1·02	68	32
9	7·75	0·04	0·45	92	8
10	2·75	0	0·76	100	0
Mean	—	0·12	1·09	87	13

Table 2. Continued

Serial tampon numbers	Duration of insertion (h)	Fluid secretion (g/h)	Blood (g/h)	Blood (%)	Fluid secretion (%)
Subject 5					
1	3·5	0·47	0·43	48	52
2	4	0·25	1·30	84	16
3	7·5	0·18	0·85	83	17
4	4	0	1·58	100	0
5	4·25	0·09	0·47	84	16
6	2·5	0·21	0·84	80	20
7	1	0·47	0·80	63	37
Mean	—	0·23	0·90	77	23
Subject 6					
1	2	0·67	1·1	62	38
2	3	0·50	1·2	71	29
3	4	0·26	0·93	78	22
4	4·5	0·11	0·60	85	15
5	2	0	1·35	100	0
6	2·5	0·27	1·48	85	15
Mean	—	0·30	1·11	80	20
Subject 7					
1	3·75	0·31	0·75	71	29
2	4·5	0·28	0·27	49	51
3	3·25	0·14	0·18	56	44
4	9·75	0·22	0·16	42	58
5	1	0·08	0·30	79	21
6	3	1·06	0·33	24	76
7	3·75	0·18	0·11	38	62
8	10·5	0·16	0·06	27	73
9	4	0·13	0·12	48	52
10	4	0·32	0·10	24	76
Mean	—	0·29	0·24	46	54
Subject 8					
1	4	0·18	0·07	28	72
2	2	0·32	0·04	11	89
3	8	0·11	0·01	8	92
4	6·5	0·19	0·06	24	76
5	3	0·34	0·23	40	60
6	1·5	0·42	0·51	55	45
Mean	—	0·26	0·15	28	72

A few negative values for fluid secretion were obtained in subjects 2, 4, 5 and 6 because of the correction used to convert total secretion weight into a fluid secretion weight (see text). These are shown as zero absorption. Subjects 1, 2, 3, 4, 5 and 7 began tampon insertion on Day 1 of their cycle while subjects 6 and 8 began on Day 2.

Table 3. Mean and median amounts and percentages of blood and fluid secretions absorbed on tampons in eight subjects*

Subject	No. of tampons	Fluid secretion (g/h) Mean	Fluid secretion (g/h) Median	Blood (g/h) Mean	Blood (g/h) Median	Blood (%) Mean	Blood (%) Median	Fluid secretion (%) Mean	Fluid secretion (%) Median
1	6	0·45	0·40	0·71	0·66	61	60	39	40
2	7	0·35	0·38	1·45	0·80	81	86	19	14
3	9	0·48	0·44	0·41	0·30	46	41	54	59
4	10	0·12	0·11	1·09	1·05	90	91	10	8
5	7	0·23	0·21	0·90	0·84	80	83	20	17
6	6	0·30	0·27	1·11	1·15	79	82	21	18
7	10	0·29	0·20	0·24	0·17	45	45	55	55
8	6	0·26	0·26	0·15	0·07	37	26	63	74
Grand means	61	0·31	0·28	0·76	0·63	65	64	35	36

*The mean and median amounts and the median percentages were calculated from the individual data listed in Table 2. The mean percentages were calculated from the mean amounts of fluid and blood listed in Table 3

It should be stressed that our subjects were asked to insert and remove the tampons according to their personal preferences and habits. The data obtained thus reflect normal tampon usage in our eight subjects and indicate the blood/secretion ratios in a healthy, young, female population using this particular tampon. Surprisingly little appears to have been published about tampon usage (see review by Reame 1983) and the cues or stimuli used by women to change their tampons. On questioning our subjects, they gave as reasons the actual feeling of blood (wetness) seeping on to the labia, perineum or thighs (breakthrough leakage) and experience from previous menses in relation to the amount of time that a tampon can be left in the vagina before this breakthrough leakage occurs. Some occasionally employed automatic changing of the tampon at each urination/defaecation or at specific time intervals like coffee and lunch breaks. One subject mentioned a technique used when she wished to leave a tampon in for a longer time interval than usual. She removes the tampon when sitting on the toilet and then bears down on the vagina by holding her breath and increasing the intra-abdominal pressure (Valsalva manoeuvre). This squeezes out stored blood from the uterus/vagina allowing the tampon next inserted to be maintained *in situ* for a longer period of time before breakthrough leakage. She said that many nurses used this technique if they were in situations where they could not easily change their tampons (i.e. operating theatre, social occasions, etc.). The wide variations in tampon changing behaviour will obviously influence the relation between the amount of genital fluid absorbed and the uptake of blood on the tampons.

Only one other study (Fraser *et al* 1985) has attempted to quantitate the blood lost at menstruation with the total amount of menstrual discharge collected on tampons. Using a technique, similar to ours, Fraser *et al.* (1985) collected a mean total menstrual discharge/24 h of 15·6 ml (SE 1·5) in 15 women. Approximately 34% (mean 5·3 SE 0·9 ml) of this was estimated to be blood so that the amount of genital secretion collected during menstruation was 10·3 ml. Cervico-vaginal fluid collected on tampons by 6 subjects on non-menstruating days, was assessed as 4·4 (SE 0·4) ml/24 h. Assuming a similar amount being produced during menstruation; some 5·9 ml/24 h (10·3−4·4 ml) of fluid, representing 38% of the total menstrual discharge, was unaccounted for by cervico-vaginal fluid or blood. It was suggested that the source of this unaccounted for large volume of fluid was probably uterine, it being formed mainly from endometrial tissue exudate during shedding rather than endometrial glandular secretion. The latter would presumably be quantitatively small during menstruation (Clemetson *et al.* 1973). Thus Fraser *et al.* (1985) found that blood *per se* accounted for only 36% of the total menstrual fluid discharge collected on tampons while our values indicate that some 65% of the weight was

Table 4. Amount of genital secretions produced by women collected either by absorbent material (tampons) placed in the vagina or by glutaraldehyde-treated collagen sponges or estimated by vaginal wall evaporation rate

Author	No of subjects	Genital secretions (g/24 h)	(g/h)	Secretion source*
Odeblad (1964)	12	6	0·25	Cervico-vaginal
	12	3·1	0·13	Vaginal
Dusitsin *et al* (1967)	?	2·7	0·11	Vaginal
Wagner (1979)	8	7·5 (1·3)	0·31	Cervico-vaginal
Wagner (1979)	7	9–11	0·38–0·46	Vaginal (evaporimeter)
Wagner & Levin (1980)	9	7·9	0·33 (0·14)	Cervico-vaginal
Chvapil *et al* (1985)	6	19·4	0·81	Cervico-vaginal (treated collagen sponge)
Fraser *et al* (1985)	6	4·4 (0·4)	0·18	Cervico-vaginal
Present study	8	7·4	0·31	Cervico-vaginal (during menses)

The data are means (SD) where appropriate.

*The particular days of the menstrual cycle that the fluid were collected was not stated in most studies

blood. To support their own data, Fraser *et al.* (1985) emphasised that in a number of previous studies the haemoglobin concentration of collected menstrual blood was significantly less than that of peripheral blood (Elert & Nold 1956; De Merre *et al.* 1967). A careful reading of all the methods of collection of their quoted studies, however, indicates that the menstrual blood obtained was always collected in or from the vagina by means of occlusive caps and not directly from the uterine cavity. The discharge was presumably always contaminated with an unknown amount of cervico-vaginal fluid. Various estimates of this cervico-vaginal fluid have been made (Table 4). Apart from the data of Chvapil *et al.* (1985) where the fluid was collected on glutaraldehyde treated collagen sponges which stimulated fluid production, the amount of cervico-vaginal secretion absorbed on tampons ranges from 0·18 to 0·33 g/h. The subjects reported by Fraser *et al.* (1985) produced lower mean amounts of cervico-vaginal secretions (0·18 g/h) than those in our study (0·33 g/h) and much lower amounts of blood (0·22 g/h) than our subjects (0·76 g/h). These differences, plus the fact that we corrected our secretion data for solid material may be part of the explanation for the obvious lack of agreement between the percentage amount of blood/secretions on tampons observed in the two studies. The results of the two studies, however, do illustrate the difficulty in using the gain in weight of the sanitary material (Pendergrass *et al.* 1984) as an assessment for menstrual blood loss. Factors changing the cervico-vaginal secretions and perhaps the endometrial tissue fluid loss suggested by Fraser *et al.* (1985) will clearly influence the final weight gain of the sanitary device.

A number of authors have associated vaginal damage with tampon usage (Barret *et al.* 1977; Fredrich & Siegesmund 1980; Jimerson & Becker 1980, Raum *et al* 1980; Shands *et al* 1981; Friedrich 1981; Crowder & Shannon 1983, Weissberg & Dodson 1983) Friedrich (1981) suggested that tampons can cause transient drying out of the vaginal epithelium (with subsequent damage observable at the colposcopic level) even during menstruation, by inducing excessive fluid withdrawal from the vaginal epithelium and that epithelial damage caused by tampons may aid in the development of toxic shock syndrome The effect of tampons on the morphology of the vaginal mucosa is to be described in a future publication.

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A low voltage diathermy loop for taking cervical biopsies: a qualitative comparison with punch biopsy forceps

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Summary. Twenty patients attending a colposcopy clinic because of a cytological suspicion of dyskaryosis were entered into a 'paired' biopsy study. A low voltage diathermy loop biopsy and a punch biopsy were taken from the cervix of each patient. In a second 'unpaired' study loop biopsies taken from 20 patients were compared with punch biopsies taken from 20 different patients. The length and depth of the loop biopsies were greater than those of the punch biopsies. There was no difference in the amount of artefactual damage. These findings held for both the paired and the unpaired studies. We conclude that biopsies taken with the low voltage diathermy loop are more likely to reveal microinvasive disease.

Local destructive techniques are widely used in the treatment of cervical intraepithelial neoplasia (CIN). The low morbidity of these techniques means that they are particularly suitable for treating younger women who have not yet completed their families (Briggs 1979). A prerequisite to their use is that invasive disease is ruled out. The colposcopic appearances of frankly invasive cervical neoplasia are relatively straightforward and will usually be recognized by an experienced colposcopist. The same is not true of microinvasive disease. According to Stafl (1983) the skill of a colposcopist is tested by his ability to diagnose microinvasion. Whilst cytology and colposcopy may be suggestive of CIN rather than invasive disease, only histological examination of an adequate biopsy taken from the most abnormal site within the transformation zone can rule out invasive disease with confidence. Also a histological opinion is limited by the quality of the biopsy presented to the pathologist. Colposcopically directed biopsies are usually taken without analgesia and using punch biopsy forceps. In our experience, the pathologist sometimes finds it difficult to make a definitive diagnosis on the basis of punch biopsy specimens. Cartier *et al.* (1981) has described his experience with a low voltage diathermy loop for both taking biopsies and for excising the transformation zone of patients with CIN. We have compared the quality of biopsies taken using a low voltage diathermy loop with those taken using our usual punch biopsy forceps.

Subjects and methods

The punch biopsy forceps used in this study were the Yeoman's rotating biopsy forceps. The low voltage diathermy machine that we used was the Surgilec 130 which allows cutting and coagulation at a power output of up to 200 W. It is made in France and cost FF 6003.30 in 1983. It satisfies current British safety standards requirements. The actual loops (Fig. 1) were made by the Medical Physics Department at the Bristol General Hospital using 0·20 mm steel (Ormiston, London, ref. 316S16).

Subjects were recruited from new referral patients attending a once-weekly colposcopy clinic These women are usually referred on the advice of the cytology laboratory because of a

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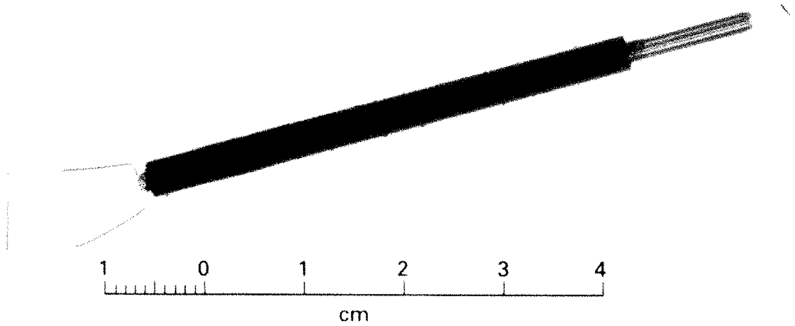

Fig. 1. Diathermy biopsy loop.

cytological suspicion of dyskaryosis. As part of their routine colposcopic investigation two or more biopsies will usually be taken from the most apparently dysplastic areas within the transformation zone.

We undertook two separate studies. In the first, a loop biopsy and a punch biopsy were each taken from the same patient at the same initial colposcopic examination. This study we hereafter refer to as the 'paired biopsy' study; it comprised 20 patients. It is possible that observer bias might play a role in such a study. In an attempt to eliminate this bias, a further study was undertaken. In this 'unpaired study' the loop biopsies taken from a further 20 patients were compared with punch biopsies taken from 20 patients before the low voltage diathermy loop machine was available. In this study the punch biopsy specimens examined were the 'best' biopsy specimens the colposcopist achieved using the punch biopsy forceps.

Sections were cut at 2–3 levels for routine diagnosis and were reassessed by one observer (J.B.) who had no knowledge of the biopsy technique used or the patient's history. The optimum level was scored as follows:

Length. The maximum length of the biopsy was measured along an axis parallel to the surface using a calibrated micrometer eyepiece.

Depth. The maximum depth of the biopsy was measured at right angles to the surface using the same technique.

Gland score. The presence of endocervical glands was scored subjectively from 0 to 3 according to the following system: no glands, 0; a few glands, 1; many glands, 2; biopsy includes base of glands, 3.

Artefact score. The amount of artefact was assessed subjectively, no attempt being made to distinguish between crush and diathermy artefact. Scores from 0 to 4 were assigned as follows: no artefact, 0; mild artefact, 1; moderate, 2; severe, 3; unreadable biopsy, 4.

Results

The data obtained for each of the biopsies examined are shown in Tables 1 and 2. The length and depth of the loop biopsy specimens were greater than those of the punch biopsies and the differences were statistically significant. This difference was maintained in both the paired and unpaired studies. Also in both studies the gland score was greater in the loop biopsy specimens but the difference did not reach significance at the 5% level in the unpaired study. There was no statistical difference between the loop and the punch biopsy specimens when examined for artefactual damage and this was true in both the paired and unpaired studies. However, the artefactual damage was of a different nature in the loop and punch biopsy specimens. In the loop specimens there was often quite extensive diathermy artefact affecting the surface epithelium and this made assessment of surface changes more difficult. In the punch biopsy specimens cytological detail in epithelial cells was usually excellent, but they sometimes showed considerable stripping of surface epithelium.

Discussion

The diagnostic accuracy of colposcopy in terms of accurately predicting the true histological picture may reach beyond 85% in experienced hands (Stafl & Mattingly 1973). However, it is not possible to know how many cases of microinvasive disease are missed without performing cone biopsies in all patients with colposcopic evidence of CIN. In the study by Choo *et al.*

Table 1. Paired biopsy study

Patient	Length (mm)		Depth (mm)		Gland score (0–3)		Artefact score (0–4)	
	Loop	Punch	Loop	Punch	Loop	Punch	Loop	Punch
1	5·8	2·8	4·0	1·8	1	1	1	1
2	6·3	2·0	4·3	1·3	2	1	1	1
3	5·8	2·5	5·1	3·0	2	2	3	1
4	5·3	4·8	7·3	1·8	3	1	2	1
5	4·5	3·0	3·7	2·5	3	1	2	3
6	4·0	2·3	4·8	0·25	3	0	2	1
7	7·6	2·3	2·8	0·5	2	1	2	1
8	5·6	2·8	3·5	2·5	2	1	2	1
9	4·3	2·5	7·1	1·3	2	2	2	1
10	5·3	3·0	2·8	0·5	2	0	3	1
11	4·8	3·3	5·3	2·2	2	1	2	2
12	6·3	4·3	2·8	1·3	2	0	1	1
13	4·8	2·5	2·8	2·5	1	1	2	1
14	2·5	5·1	3·0	0·2	1	1	2	1
15	3·8	1·3	5·8	1·0	2	1	3	1
16	4·8	3·0	2·5	1·8	1	2	2	1
17	6·1	1·8	2·5	0·5	2	0	2	3
18	3·8	2·3	1·3	1·0	0	1	2	1
19	3·0	3·0	7·1	0·2	2	0	3	2
20	7·3	3·3	5·6	2·5	2	0	1	1
Mean	5·1	2·9	4·2	1·4	1·8	0·8	2·0	1·3

Significance of differences between loop and punch biopsies: for length $P<0{\cdot}0001$ (paired t-test), for depth $0{\cdot}02>P<0{\cdot}01$ (paired t-test); for gland score $P<0{\cdot}01$ (Mann–Whitney test); for artefact score $P>0{\cdot}05$ (Mann–Whitney test)

(1984) a correct colposcopic diagnosis was made in only seven (27%) of 26 patients with microinvasive disease. They used Tischler biopsy forceps which they claim will often yield a wedge of tissue more than 0·5 cm in depth. In our paired study there were no cases of microinvasive disease and the histological information gained from the loop biopsies did not differ such that management of any of these patients was changed as a result. But we would not expect to find a case of microinvasive disease in such a small sample of patients.

However, since adopting the loop for routine use we have made the diagnosis of microinvasive disease in four patients during 1985 (January to July) compared with only one for the same period in 1984. Furthermore, in all four it was possible to make the diagnosis from the loop biopsy rather than at cone biopsy. We are fully aware that this may be due to chance, increasing observer experience or a genuine increase in the prevalence of microinvasive disease, rather than that we had missed cases in 1984.

The important factors that allow the pathologist to give a reliable opinion are that the biopsies be large enough (Anderson & Hartley 1980); not damaged by the technique used to take them and taken from the most atypical area in the transformation zone. Additional clinical factors that should be considered when trying to assess the optimum biopsy technique in the colposcopy clinic are the degree of blood loss, the amount of discomfort with which a particular method is associated, and the time it takes to perform. This study reveals the superiority of the low voltage diathermy loop machine in taking larger biopsies without an increase in the amount of artefactual damage. The artefactual damage associated with the loop is qualitatively different when compared with punch biopsies

We have gained the clinical impression that the loop biopsy technique is associated with a greater degree of discomfort than punch biopsies. Also the loop does not always coagulate the biopsy bed sufficiently well to control bleeding. However, it has always been possible to control this bleeding by switching the cutting modality to coagulation or by applying silver nitrate to the

Table 2. Unpaired biopsy study

Loop biopsies					Punch biopsies				
Patient	Length (mm)	Depth (mm)	Gland score (0–3)	Artefact score (0–4)	Patient	Length (mm)	Depth (mm)	Gland score (0–3)	Artefact score (0–4)
1	7·8	4·3	2	2	21	3·0	2·5	2	1
2	11·4	6·3	3	1	22	2·8	2·4	0	1
3	7·1	2·8	0	3	23	2·5	0·9	0	1
4	5·6	3·5	2	2	24	2·5	0·8	0	1
5	5·8	2·2	2	1	25	2·2	1·5	2	2
6	5·8	3·8	2	2	26	3·0	3·0	1	1
7	4·7	2·3	2	2	27	2·5	0·2	0	2
8	5·1	2·9	1	2	28	2·6	1·6	0	1
9	5·8	2·3	0	1	29	2·5	0·9	0	1
10	4·0	1·8	1	1	30	3·3	2·5	1	2
11	5·2	4·8	3	1	31	1·3	0·6	0	2
12	4·7	4·5	1	1	32	2·6	1·9	1	1
13	2·5	6·8	2	2	33	4·0	2·0	1	1
14	4·5	2·2	1	3	34	1·8	2·1	2	1
15	8·8	1·8	1	2	35	3·3	0·5	0	1
16	4·3	2·2	0	1	36	2·8	1·2	2	2
17	3·0	3·8	3	2	37	2·3	1·4	1	2
18	6·8	3·4	1	1	38	2·8	1·8	1	1
19	4·5	2·2	1	2	39	2·3	0·5	0	1
20	5·3	1·9	1	1	40	3·4	2·5	1	1
Mean	5·9	3·3	1·5	1·7		2·9	1·5	0·7	1·3

Significance of differences between loop and punch biopsies: for length $P<0{\cdot}001$ (unpaired *t*-test); for depth $P<0{\cdot}001$ (unpaired *t*-test); for gland score $P>0{\cdot}05$ (Wilcoxon's rank sum test for unpaired samples); for artefact score $P>0{\cdot}05$ (Wilcoxon's rank sum test for unpaired samples).

wound. We have tried to overcome these problems by prior infiltration surrounding the biopsy site of 1% lignocaine with 1 in 200 000 adrenaline solution using a 26 gauge needle and dental syringe system. The total extra time involved in taking a biopsy using the low voltage diathermy loop is about 2–3 min.

In summary we feel that the low voltage diathermy loop is superior to conventional punch biopsy forceps for taking a colposcopically directed biopsy because it produces larger biopsies which are more likely to reveal microinvasive disease. These benefits outweigh the longer time taken and the need for local analgesia. We recommend that other colposcopists assess this or similar low voltage systems.

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A rare late complication of first trimester induced abortion requiring hysterectomy–subinvolution of the placental bed. Case report

E. T. C. LEE, N. J. E. MARLEY, J. R. BEVAN

Case report

A 25-year-old single woman, pregnant for the second time, was admitted to hospital for an induced abortion at 12 weeks gestation. She had had a normal pregnancy 6 years previously. There was no history of any menstrual disturbance or bleeding tendencies. The pregnancy was terminated by suction and sharp curettage with no immediate complications and she was discharged using Eugynon 30 for contraception. Nine weeks after the termination she was admitted again because of heavy vaginal bleeding. On examination she was apyrexial and not shocked. The uterus was bulky, not tender with an open cervix. The haemoglobin was 13·0 g/dl. An ultrasound scan showed small irregular cystic areas in the uterine fundus of unclear significance. A uterine curettage yielded scanty tissue which consisted of blood clot and a small fragment of endometrium showing pseudo-decidualization on microscopy. Endometritis was the assumed diagnosis and antibiotics were prescribed.

Thirteen weeks after the induced abortion, she was again admitted with sudden heavy vaginal bleeding. On this occasion the uterus was of normal size and the os was closed. The bleeding subsided spontaneously and she returned home. Two weeks later she was readmitted with irregular vaginal bleeding and flooding She was not shocked, but pale. The cervix was closed with a uterus that was bulky and tender. The haemoglobin level was 5·6 g/dl, the white cell count, platelet count and coagulation profile were all normal; a blood film was consistent with iron deficiency and blood loss. Human chorionic gonadotrophin was not detectable in a 24-h urine collection. After a transfusion, the bleeding again ceased spontaneously, she was started on oral iron and returned home. Seven weeks later she had a further episode of sudden heavy vaginal bleeding which subsided rapidly after admission. Norethisterone, 5 mg twice daily, was started on a cyclical basis. Readmission was required for the sixth time 3 weeks later because of further heavy vaginal bleeding. The dose of norethisterone was increased to 10 mg twice daily and subsequently four times daily. The bleeding suddenly worsened after 3 days, and the haemoglobin level fell from 11·0 g/dl on admission to 6·4 g/dl. The platelet count and coagulation profile were again normal. Seven units of blood were required to raise the haemoglobin to 10·0 g/dl. On the ninth day after admission she had a further vaginal bleed requiring further transfusion. On account of these frequent massive haemorrhages, a hysterectomy was performed some 6 months after the termination. Prior curettage revealed some irregularity of the uterine cavity.

On pathological examination the uterus measured 9 × 5 × 3·5 cm. The endometrium was slightly polypoid with blood clot overlying an area of prominent vessels in the body. Appropriate sections were stained with haematoxylin and eosin, Miller's elastic van Gieson, Martius scarlet blue, phloxine tartrazine and to detect periodic acid Schiff positive material Microscopy of the area of prominent vessels and of the endometrial curettings showed a mass of large, thick-walled, tortuous vessels extending from the surface, deep into the myometrium. Many of the endometrial and subjacent myometrial

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arteries were hyalinised, some with widely dilated lumens (Fig. 1). The hyalinised segments of vessels showed no evidence of muscle or elastic tissue, but in places they contained effete non-villous trophoblast-like cells (Fig. 2). These cells were not identified in other segments of vessels nor in the myometrial interstitium. The prominent vessels that protruded above the overlying endometrium contained red cells with recent platelet and fibrin thrombi. The spiral and deeper radial arteries unaffected by hyaline change showed marked focal intimal thickening that contained collagen and spindle cells, whereas this proliferation was relatively minor or absent in hyalinised vessels. Other vessels in this region had involuted completely and had small central lumens. The endometrium remote from the site of placentation showed changes consistent with exogenous hormone administration, being polypoid with reduced numbers of glands with inactive epithelium, mild pseudodecidualisation of superficial stroma and with many stromal granulocytes (K cells). No viable or hyalinised chorionic villi were identified. The findings are those of so-called subinvolution of the placental bed.

Discussion

Although maternal morbidity and mortality have decreased since the introduction of the Abortion Act of 1967, legal abortion is still associated with significant hazard. The prevalence of hysterectomy for complications arising from first trimester abortion has been reported to be between 0·01 to 0·7% (Sood 1971; Strausz &

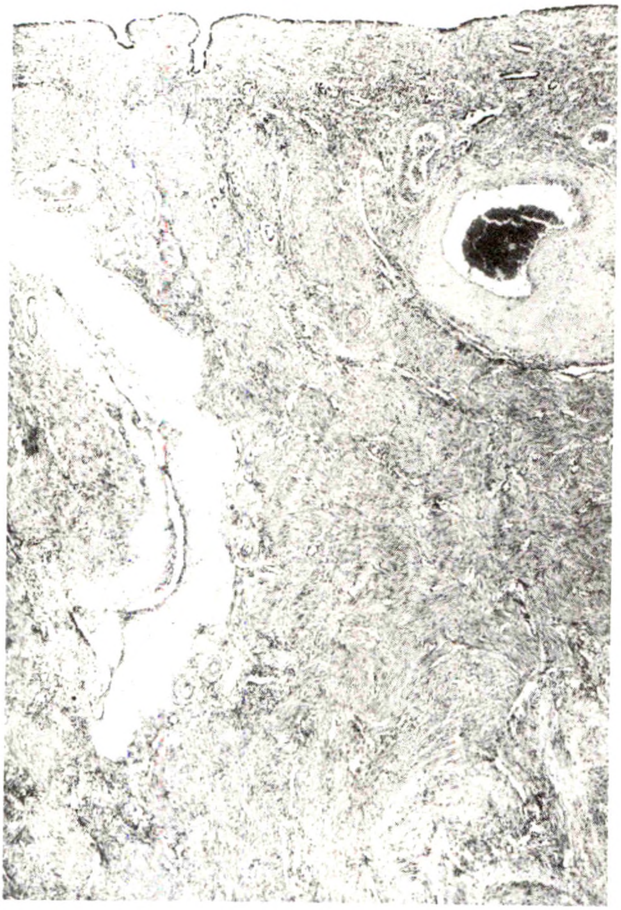

Fig. 1. Placental site arteries showing hyaline change which extends into the subjacent myometrium. One of the vessels has a widely dilated lumen (haematoxylin and eosin).

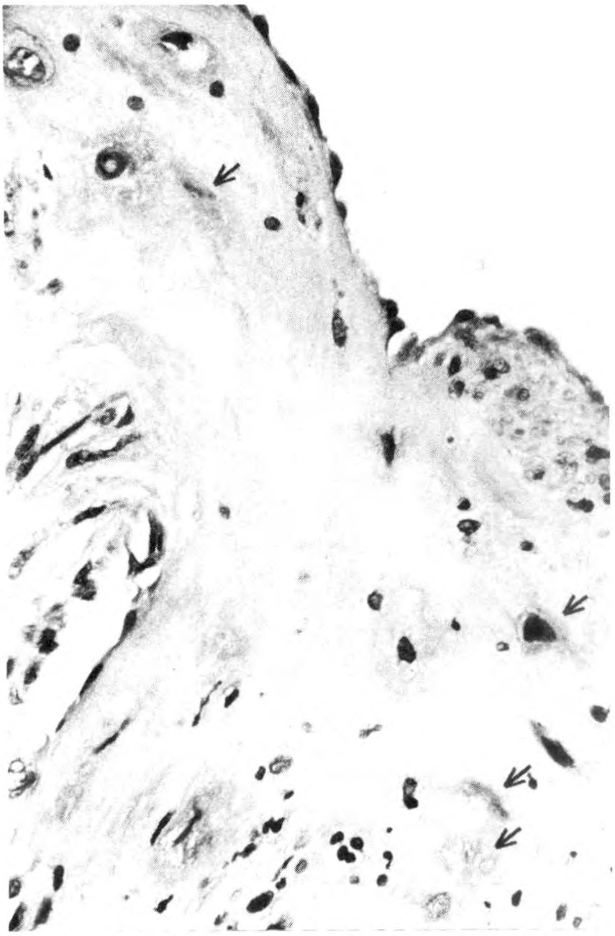

Fig. 2. Degenerate and 'ghost' forms of non-villous trophoblast-like cells (arrowed) within an area of hyaline change between two vessel lumens (haematoxylin and eosin).

Schulman 1971; Hodgson & Portmann 1974) and no pathological lesions to account for the complications were identified.

In our patient, abnormal vessels were present suggesting subinvolution of the placental site and this would appear to be an extremely rare cause of recurrent heavy bleeding following first trimester abortion.

Subinvolution of the placental site or bed is an acceptable term as it reflects the incomplete resolution of the vascular and other changes of the pregnant uterus giving rise to post-abortion and postpartum bleeding. Unfortunately, it may be confused with the ill-defined term subinvolution of the uterus, which is usually applied to the bulky uterus that persists following a number of pregnancies. Rutherford & Hertig (1945) reported three cases with clinical and pathological details defining subinvolution of the placental bed as the failure of complete physiological obliteration of the placental site vessels in the absence of retained trophoblastic tissue. They discounted chronic inflammation as a significant aetiological factor. From subsequent reports, including Gainey *et al.* (1954) and Paalman & McElin (1958), the clinical picture developed as that of 'delayed postpartum haemorrhage, abrupt in onset, occurring at any time from one week to several months after delivery and maximally during the second week of the puerperium. On examination the uterus is larger than expected, soft and boggy; the cervical os is patulous and blood trickles or pours from it' (Ober & Grady 1961). Interestingly our patient, whilst presenting with such a picture, later regained a normal-sized uterus on bimanual examination. Thus the presence of a normal-sized uterus with closed cervix does not exclude the diagnosis of subinvolution of the placental site. Ober & Grady (1961) described the pathological abnormality as that of 'a patulous lumen with perfectly or partially organizing thrombosis within a vessel, the wall of which is distorted by hyaline material'

Whether all clinical cases of subinvolution of the placental site have a common underlying pathogenesis is not known as a pathological diagnosis may be extremely difficult in the first 2 weeks postpartum. This is in part due to a lack of precise information regarding the range of variability of normal involution. The vascular changes, as well as being seen postpartum, may also occur after spontaneous (Salm & Simons 1960) and procured abortion (Ober & Grady 1961). The latter also occasionally saw retained placental tissue in association with these changes. Whether this entity is exceptional in the first trimester is not known as no gestational data were given for their cases. Curettage and blood replacement were usually adequate therapy.

Human haemochorial placentation is complex and, to establish an adequate uteroplacental circulation, two separate waves of migration of non-villous endovascular trophoblast are required to effect structural alterations to the maternal blood vessels (Robertson *et al.* 1975; Pijnenborg *et al.* 1983). This results in the transformation of the spiral arteries of the normal placental bed into uteroplacental arteries. The first wave finishes at the endomyometrial interface while the second endovascular migration occurs a few weeks later and extends down into the myometrial segments of the spiral arteries, often as far as their origin from the more distal radials. Although this second wave was initially reported as commencing at about 12–16 weeks gestation (Robertson *et al.* 1975) and endovascular trophoblast may even be seen at 10 weeks in a few superficial myometrial spiral arteries, it really only gets underway at 16–18 weeks gestation (Pijnenborg *et al.* 1983). The process of spiral arterial transformation involves the migration of trophoblast, along with subsequent incorporation, into the intima of the arteries (Brosens *et al.* 1967; Pijnenborg *et al.* 1983). Muscle and elastic loss are seen in arteries invaded by trophoblast where it is also accompanied by fibrinoid change to produce the so-called physiological vascular changes (Brosens *et al.* 1967). This fibrinoid change appears to undergo hyalinisation in the involutionary process following pregnancy (Ober & Grady 1961; Robertson 1981) and thus these vascular features can be considered to indicate the uteroplacental vessels that had been transformed by the action of migratory trophoblast. The pathological lesion of subinvolution of the placental bed is found only in vessels affected by the physiological changes of pregnancy and it is of interest that in our patient the abnormality also involved myometrial vessels before the second wave of endovascular trophoblast migration should have commenced.

The disparity in our patient between the estimated gestation and the onset of the second wave is possibly due to the gestational age being incorrect, but it should not be dismissed as such. The mechanisms that are responsible for the onset, cessation and disappearance of trophoblastic invasion are not understood. Neither is the mechanism of subinvolution. Other possibilities should be considered, such as an early second wave of endovascular trophoblast migration or even the unlikely possibility that a further pregnancy progressing to at least 16 weeks occurred in the intervening 6 months. Alternatively, non-villous trophoblast left behind after the termination subsequently invaded the myometrial spiral arteries which could then represent an endovascular type of benign persistent trophoblast disease. Certainly effete non-villous trophoblast-like cells were seen in the hyalinised vessel walls but their presence is more likely to be simply due to a failure of removal of the hyalinised material so that the cells remained sequestered in the vessel wall. It is, nevertheless, remarkable that these cells were present as non-villous trophoblast including placental bed giant cells usually disappear within the first 2 weeks postpartum (Boyd & Hamilton 1970). Finally the rarity of the lesion could be explained also by the pre-existence of an intrauterine vascular abnormality which happened to be the site of implantation, but this seems unlikely, due to the apparent normality of the pregnancy until termination, nor does it take account of the involvement of the myometrial arteries by hyaline change.

More importantly, however, we are struck by the absence of reports of subinvolution following pregnancies that have ended before the second wave of endovascular trophoblast migration should have commenced. This, together with evidence that the myometrial spiral arteries have been involved by the physiological changes of the second wave suggests to us that this wave is an essential component in the pathogenesis of this lesion. Furthermore, if this is the case, subinvolution would be expected not to occur in pregnancies complicated by pre-eclampsia where it has been shown by Brosens *et al* (1972) that the second wave does not appear to take place.

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BOOK REVIEWS

The Y Chromosome. Part A: Basic Characteristics of the Y Chromosome 608 pages with figures and tables £155.00 **Part B: Clinical Aspects of Y Chromosome Abnormalities** 408 pages with figures and tables £112.00 (Progress and Topics in Cytogenetics Volumes 6A & 6B) edited by A. A. Sandberg. Alan R. Liss Inc., New York, 1985

When I was a medical student, I can remember being asked in finals what genes were on the Y chromosome. The 'correct' answer was 'hairy ears'; genes for sex determination did not count apparently. Medical science seems to have moved on, as we now have a two volume collection of papers on the Y chromosome edited by Avery A. Sandberg. Part A covers the basic characteristics of the Y chromosome including cellular and molecular aspects, physical characteristics, and physiological aspects, whilst Part B covers clinical aspects of Y chromosome abnormalities. The latter volume will be of most use to the clinicians, especially the chapters on the XYY syndrome, which can pose a counselling dilemma, if detected at amniocentesis. XYY males do have a slightly lower IQ than their sibs, may tend to be tall, and have an increased risk for language development problems, school problems and some behavioural problems, which in adults may be expressed as lack of impulse control. However, it appears that the original fears that many XYY males are aggressive and show criminal behaviour do not have a strong basis.

The rate at which molecular biological techniques are being applied to the Y chromosome is so rapid that I suspect some of the chapters in Part A are already out of date For example, the statement on page 111 that 'the evidence is strongly against frequent or obligatory X:Y recombination' is clearly incorrect, as this very phenomenon has been demonstrated by the use of DNA probes.

The quoted price for the two volumes, which comes to £267, seems incredible. These volumes are clearly only intended to be purchased by major academic institutions Few departmental libraries could justify obtaining a copy.

Robin M. Winter

Clinical Biochemistry of Steroid Hormones Methods and Applications by J. K. Grant & G. H. Beastall. Croom Helm Ltd, Amsterdam, 1983, 303 pages with figures and tables, £19.95

The authors of this book have spent many years at the receiving end of requests for steroid hormone assays. They know only too well how much reproductive endocrinologists (and the lesser breeds out with this charmed circle) know of what goes on in a steroid laboratory. Although they do not explicitly say so, I infer that what they set out to do was to make good the deficit. What they have produced is a book which has as much a place on the laboratory bench as on the clinician's bookshelf. It is an admirable *vade mecum* for technicians and for those of us who, for the purposes of a research project or a degree, have to dabble in laboratories. Even for more expert people the 15 appendices on definitions, molecular weights and assay methods for a variety of adrenal and ovarian steroids provide a useful quick reference source. It is a pity the authors did not think to add a small table on the conversion of molar units to weight and vice versa. The Americans are likely to keep up their resistance to SI units for quite a few years yet.

In some minor respects they can be adversely criticized for taking up a stance somewhere in mid-Atlantic. It was an unhappy surprise to come across estrogens and to find kit assay prices judged in dollars in what is essentially a British, not to say Scottish, publication. In the matter of gonadotrophins they are less certain; sometimes it is gonadotropins and at others gonadotrophins. Tumours and the like have, however, stayed resolutely on this side of the Atlantic

The first three chapters are on theoretical aspects and have to compete with the many extensive tomes in this field They are clearly written and surprisingly helpful; explaining simply such concepts as binding affinity, of which the non-biochemical reader has an uncertain grasp.

Laboratory techniques are changing fast. The date of publication (1983) is well concealed; an old publishers trick. I think that if the authors were writing the book today they would pay more attention to enzyme immunoassay and to the use of kits. Both have assumed dominant roles in laboratory practice and deserve a more detailed consideration of their advantages and disadvantages.

This book neatly fills a gap. In spite of its occasional transatlantic leanings it fits closely the needs of the British laboratory. It should be in every laboratory doing hormone analyses. It is part of a mechanism which keeps open the door between the laboratory and the ward.

Arnold Klopper

Born Unequal. Perspectives on Pregnancy and Childrearing in Unemployed Families published by the Maternity Alliance, 59–61 Camden High St, London NW1 7JL, 1986, 70 pages, £2.50

Born Unequal is a report published by the Maternity Alliance looking from different perspectives at pregnancy and child rearing in unemployed families. In four sections the experience of unemployed families, the benefits available to them and the statistics relating to unemployment and perinatal and infant health are reviewed. From these differing standpoints, the message comes across strongly that inequality exists in Britain in the 1980s as it did in the 1930s and that more than one and a quarter million children are being brought up in families where the need was unemployed and claiming benefit.

The existing allowances (recently increased slightly) are totally inadequate—for example the £25.00 Maternity Grant, if it was restored to the value of its last updating in 1969, would now be £130, which would still be below the level of many European countries. One can be critical about the unrepresentative nature of the sample of the Maternity Alliance's own study (a fact that they mention) but one cannot escape from the problems of poverty described by those interviewed. The small study from the Midlands by McKee discusses the problem of interpreting data on unemployment and the family. She found that financial hardship was the common experience of the 17 families in her study and stresses the fact that those she interviewed felt that the lack of a job was no reason for not having children. A well-argued section on benefits looks at the existing benefits and the problems with means testing. Role demonstrates that there are elements in the Social Security system which could provide the foundation for benefits paid according to need rather than income.

The section looking at the evidence about the effects of unemployment on mothers and babies' health since the depression of the 1930s, highlights the difficulties of looking at unemployment *per se* but stresses that analyses of this trend give no grounds for the claims that pregnancy outcome is not affected by unemployment. They conclude that there is need for more research into the effects of unemployment on pregnant women and their babies, but state that this must not be used as a reason for not dealing with the underlying problem.

The report on 'Inequalities in Health' [Townsend, P. & Davidson, W. (1982) Penguin Books Ltd, Harmondsworth] stated that 'we consider that the abolition of child poverty should be adopted as a National seal for the 1980s. We recognize that this requires a redistribution of financial resources far beyond anything achieved by past programmes, and is likely to be very costly'.

It is now 1986 and conditions are worse now than when that recommendation was made. The Maternity Alliance report *Born Unequal* should be required reading for all those who provide health care for unemployed families so that they (the providers of care) can begin to understand some of the problems of poverty and speak out against it.

Gillian M. McIlwaine

In Vitro Fertilization and Embryo Transfer (Annals of the New York Academy of Sciences Volume 442) edited by Markku Seppala & R. G. Edwards The New York Academy of Sciences, New York, 1985, 619 pages fully illustrated, $140.00

Since the first child was delivered following in-vitro fertilization (IVF) and embryo transfer, now almost 8 years ago, the technique has been established worldwide and success rates have been gradually improving. Research and clinical interests in this field continue to produce a demand for new information, both scientific, concerned with the basis of reproductive biology, and practical, covering the clinical aspects of the procedure. The Third World Congress on In-Vitro Fertilization and Embryo Transfer convened in Helsinki in May 1984 was intended to meet these needs and the articles in this book are based on papers presented at that meeting. All aspects of IVF are covered from detailed biological studies of follicular growth and oocyte maturation, practical techniques of oocyte recovery and embryo transfer in addition to pertinent aspects of male infertility. The psychological stress of the treatment regimens on couples is considered and genetic and ethical aspects are reviewed.

Whilst the volume presents the research and results of many of the major investigators in the field, being essentially a collection of individual papers there is inevitability overlap in certain areas and a disjointed format. The book's price (£120.00) may also be prohibitive for individuals but certainly it would be a useful book for centres undertaking IVF to have on their library shelf.

R. W. Shaw

Books received some of which may be reviewed at a later date

Pregnancy Care: A Manual For Practice edited by Geoffrey Chamberlain & Judith Lumley. John Wiley and Sons, Chichester, 1986, 278 pages with figures and tables, £14.95

Diagnosis and Management of Female Pelvic Infections in Primary Care Medicine edited by Sebastian Faro. Williams & Wilkins, London, Baltimore, 1986, 219 pages with figures and tables, £36.00

Clinical Diagnostic Ultrasound edited by E. Barnett & P. Morley. Blackwell Scientific Publications, Oxford, 1986, 617 pages illustrated, £120

Scientific Foundations of Obstetrics and Gynaecology Third Edition edited by Elliot E. Philipp, Josephine Barnes & Michael Newton. William Heinemann Medical Books, London, 1986, 646 pages illustrated, £59.95

Behavioral Teratology by E. L. Abel. Greenwood Press (distributed in Europe by Westport Publications Ltd, London), 1986, 206 pages, £35.00

Clinics in Obstetrics and Gynaecology Vol 12 No 4 New Clinical Issues in In-Vitro Fertilization edited by C. Wood & A. Trounson. W.B. Saunders Company, London, Philadelphia, 1986, 753–925 pages with figures and tables, £13.50

Obstetrics and the Newborn. An Illustrated Textbook. Second British Edition by Norman A. Beischer & Eric V. Mackay. Bailliere Tindall, London, Philadelphia, 1986, 770 pages with figures and tables (Available from Holt-Saunders Ltd Eastbourne), £14.95

Obstetric Anaesthesia and Analgesia Third Edition by Donald D. Moir & John Thorburn. Bailliere Tindall, London, Philadelphia, 1986, 389 pages with figures and tables, £17.95

Surgery of Female Incontinence Second Edition edited by Stuart L. Stanton & Emil A. Tanagho. Springer-Verlag, Berlin, 1986, 285 pages with 229 figures, DM 160

Textbook of Laparoscopy by Jaroslav Fabian Hulka. Grune Stratton Inc., Orlando, 1986, 152 pages illustrated, $49.50

Practical Obstetrical Ultrasound by John W. Seeds & Robert C. Cefalo. Aspen Publishers, Maryland (distributed through Costello, Tunbridge Wells), 198 pages with figures and tables, no price given

Flagyl. The Story of a Pharmaceutical Discovery by J. A. McFadzean. Parthenon Publishing, Carnforth, Lancashire, 1986, 117 pages illustrated, £9.95

Coping with Abortion by Alison Frater & Catherine Wright. W. & R. Chambers, Edinburgh, 1986, 88 pages illustrated, £2.95

Abortion: The Crisis in Morals and Medicine by Nigel M. de S. Cameron & Pamela F. Sims. Inter-Varsity Press, 1986, 158 pages, £2.25

Proceedings and Symposiums

Papillomaviruses (Symposium on Papillomaviruses held at the Ciba Foundation, London, July 1985) edited by David Evered & Sarah Clark. John Wiley and Sons, Chichester, 1985, 259 pages with figures and tables, £27 50

Forthcoming RCOG meetings in 1986

24th September	Scientific Meeting "Longterm effects of oral contraception"
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20th/21st October	Educational Course "Gynaecological Endocrinology"
29th October	Combined meeting with the British Association for Perinatal Paediatrics – Leicester
17th/18th November	Educational Course "Colposcopy Course"
1st – 5th December	"Consultants' Conference"

Further details are available from:- **Miss Beryl J Stevens, Postgraduate Education Department, Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London, NW1 4RG.**

Breast Cancer: Treatment and Prognosis

1986. 352 pages, 31 illustrations. £39.50

In a critical and realistic manner, this book examines the final aims in any treatment of breast cancer. It looks at the chances of achieving these aims, the price to be paid by the patient and the prospects of more effective treatment likely to become available in the foreseeable future Effective treatment of breast cancer must begin with the recognition of clinical and biological criteria of prognosis in each patient and the likelihood of response to each type of therapy The vast majority of current publications on the topic are concerned with comparisons of different types of therapy in large groups of patients, but this book places the emphasis firmly on the individual patient

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Altman, D G., Gore, S M , Gardner, M J & Pocock, S J (1983) Statistical guidelines for contributors to medical journals *Br Med J* **286**, 1489–1493

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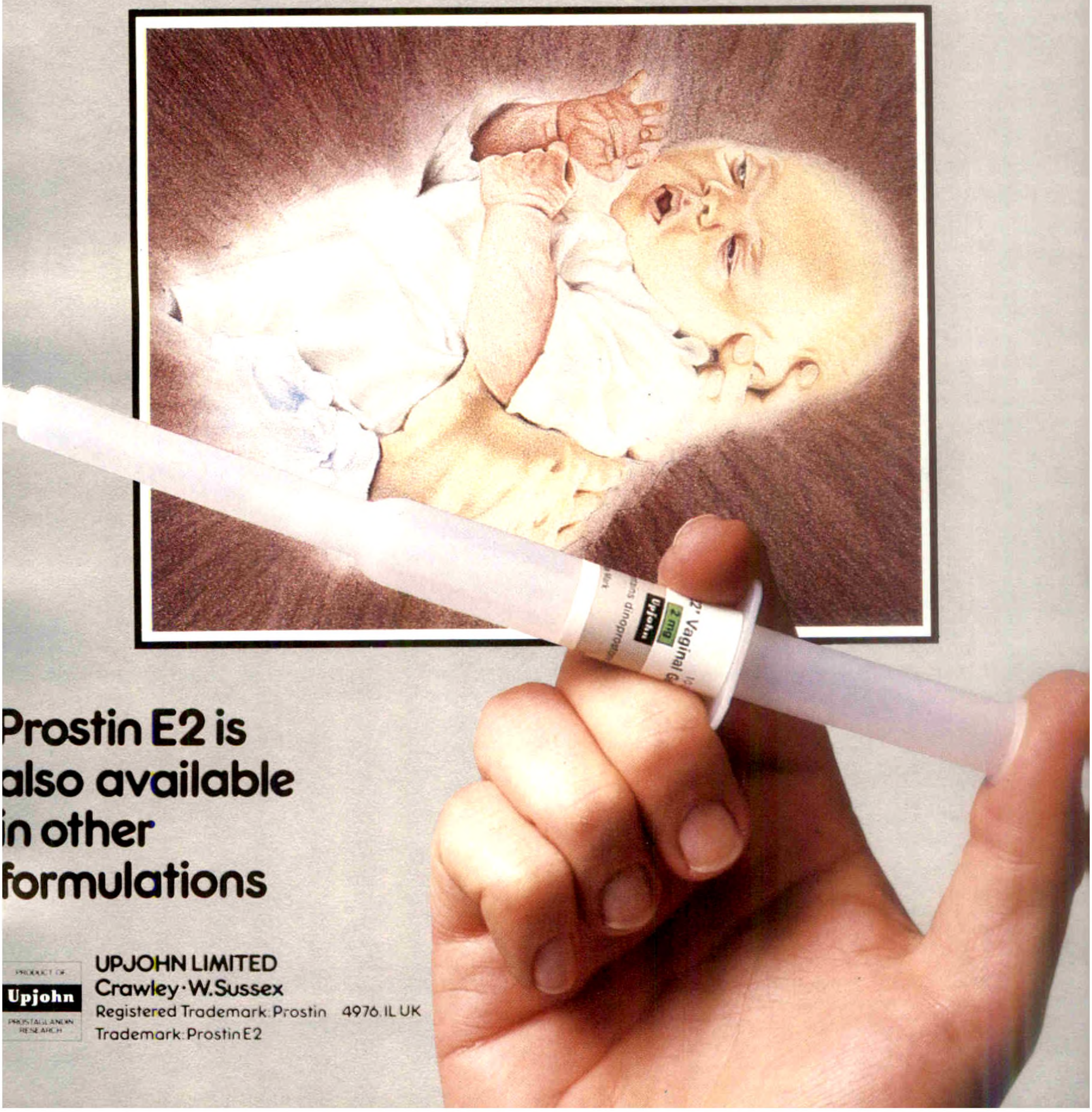

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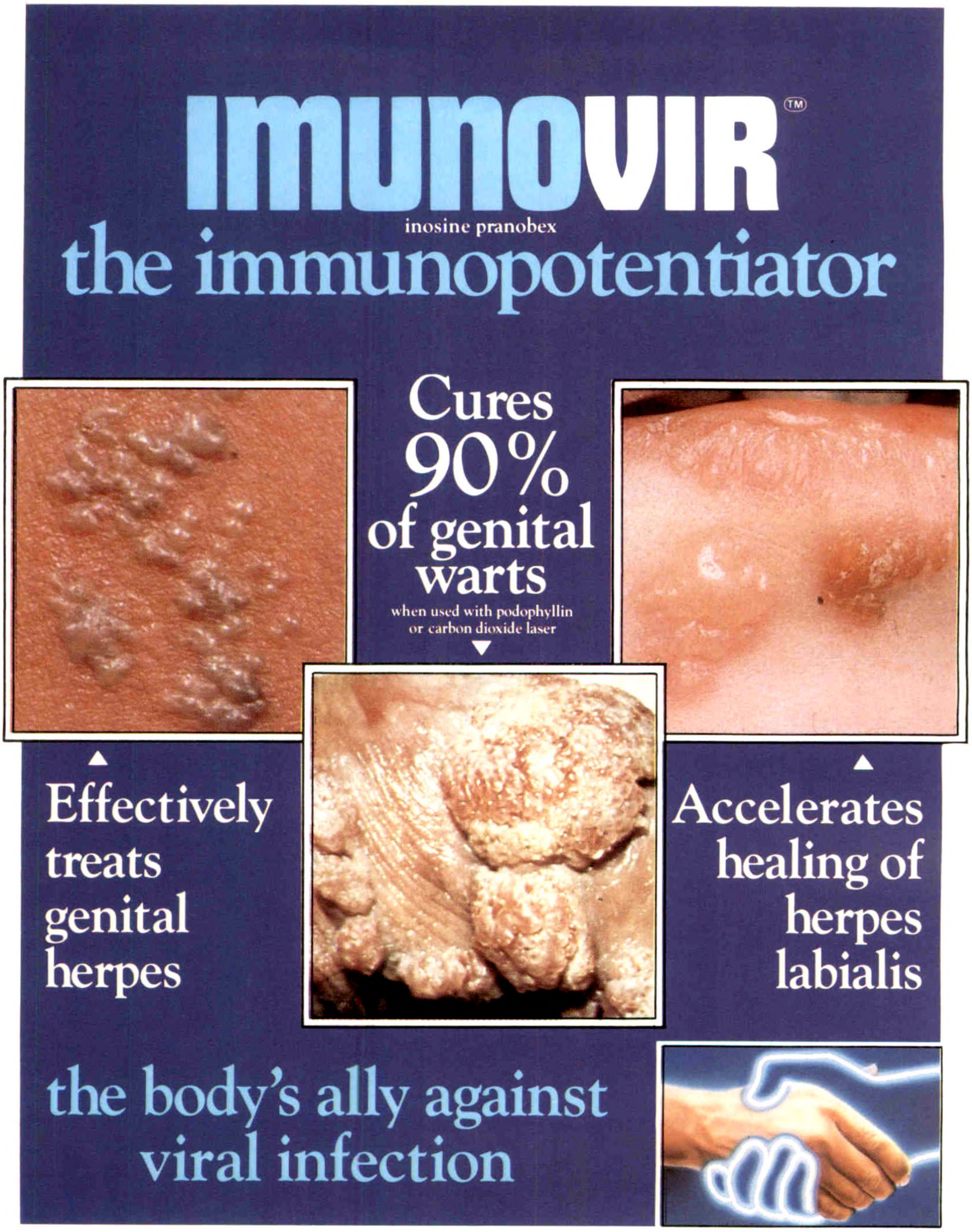

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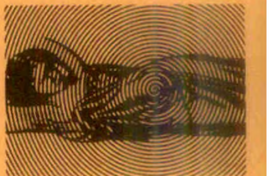

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Edited by **W.R. Jones**
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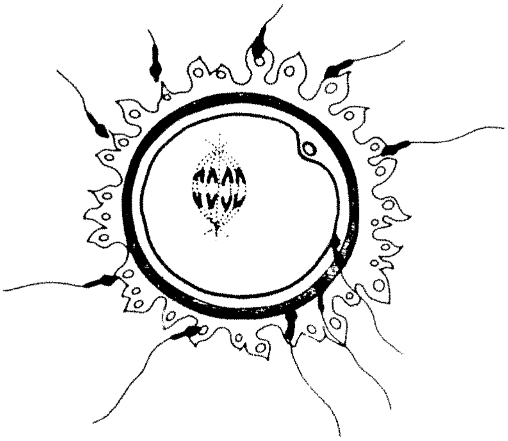

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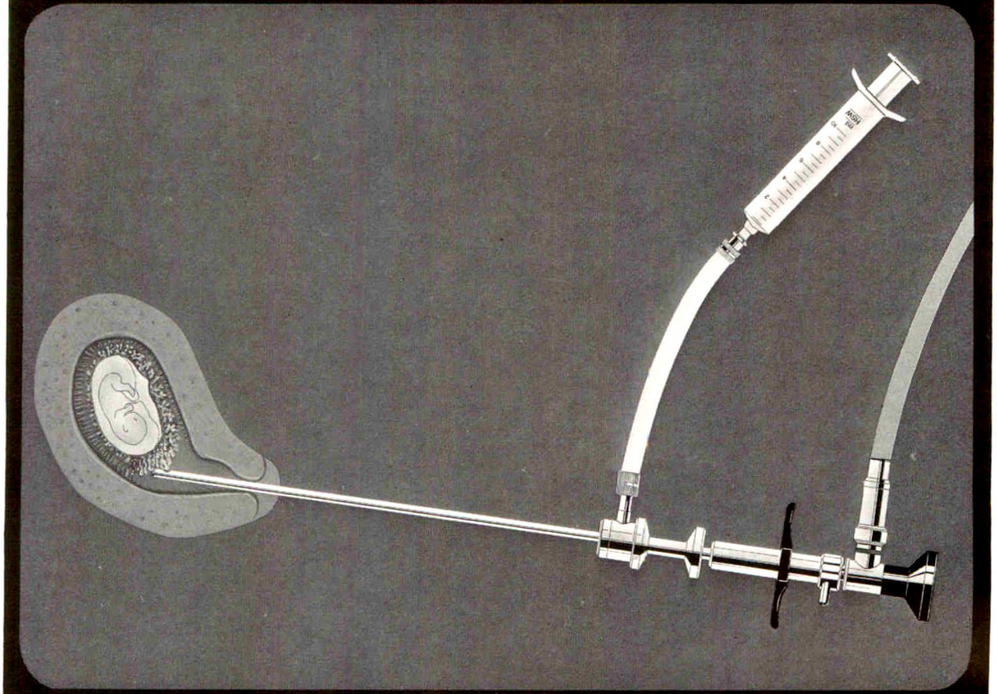

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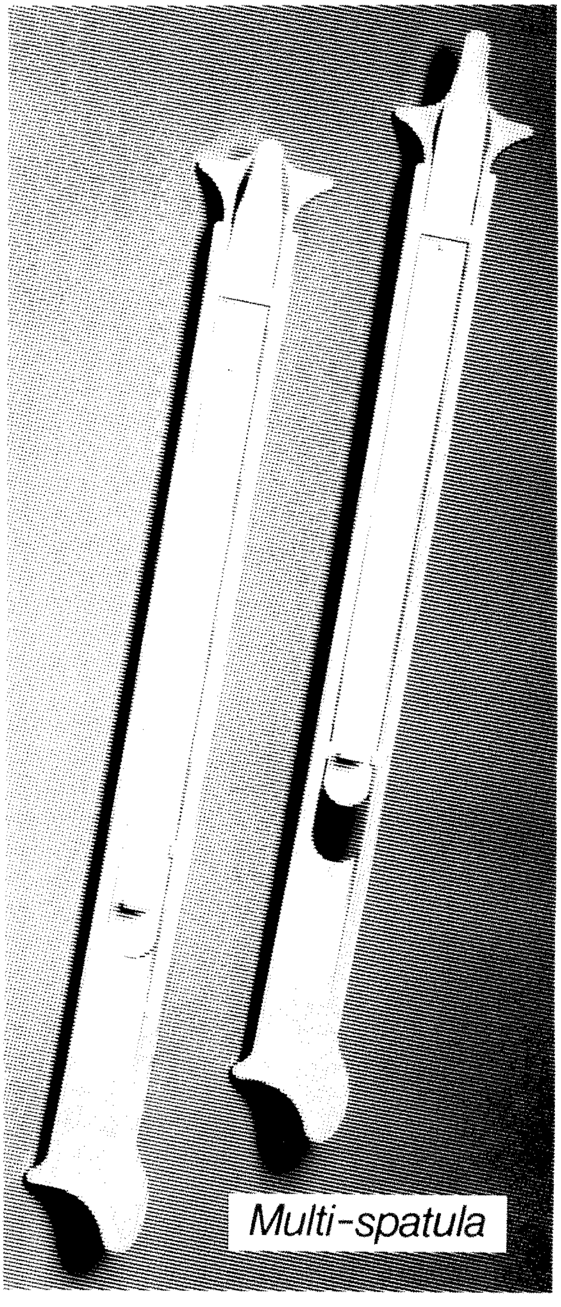

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British Journal of Obstetrics and Gynaecology
August 1986, Vol. 93, pp 785–786

COMMENTARY

Vulvar carcinoma in pregnancy

The occurrence of carcinoma of the vulva in a pregnant woman is extremely rare, mainly because the mean age for carcinoma of the vulva to present is in the late seventh decade of life The cancer does occur much more frequently in younger women in its intraepithelial form (VIN) often presenting difficult diagnostic and management problems. The relation between VIN and the invasive lesions seen in older women is unclear; the pre-cancer is usually multifocal whereas the invasive type seen in older women is almost always unifocal.

In the pregnant patient presenting with vulvar irritation which cannot be attributed to infection, it is important to biopsy any suspect area and not to delay until the postnatal period. If there are ominous signs such as fissuring, raised areas or ulcers a biopsy is essential. Currently it is fashionable to perform colposcopy on the vulva. This procedure can be of considerable value when used with the application of dilute acetic acid; it is not so successful when used with toluidine blue. Colposcopy assists the clinician in defining the area to be biopsied.

The biopsy should be of sufficient size for the pathologist not only to comment on the histopathological pattern but also on the depth of invasion of the tumour. Reports of the degree of lymphocytic reaction, degree of confluency, lymphatic channel or vascular space involvement are not of great value.

Treatment

The most important factors to be taken into account when determining the extent of treatment are the size and site of the tumour and the depth of invasion (Monaghan 1985). Local excision biopsy should only be used for lesions where the depth of invasion is less than 1 mm (Hacker *et al.* 1984).

In patients with Stage I (< 2 cm in diameter) laterally placed tumours, a radical vulvectomy with an ipsilateral groin node dissection should be performed through separate incisions. For Stage I disease encroaching on mid-line structures, and for later stage disease with carcinomas up to 4 cm in diameter, a radical vulvectomy with bilateral groin node dissection should be performed through separate incisions.

For carcinomas greater than 4 cm in diameter a pelvic node dissection should be added to the groin node dissection and the groins should be dissected *en bloc* in direct continuity with the radical vulvectomy, utilizing a modified 'Butterfly incision'. Where the cancer extends onto the anus or lower rectum an anovulvectomy should be performed together with groin and pelvic node dissection (Monaghan 1986).

Clearly, utilizing these recommendations there is a great opportunity to individualize treatment. The management of the disease in this way does not significantly affect the pregnancy. Even when it is necessary to perform a pelvic node dissection the procedure can be carried out without jeopardizing the pregnancy.

Timing of surgical treatment. If the carcinoma is diagnosed at any time up to 36 weeks gestation definitive treatment can be performed in pregnancy. If the diagnosis is made later than that, delay into the puerperium will not seriously prejudice the course of the disease.

Mode of delivery. Many obstetricians are nervous about allowing vaginal delivery after vulvar surgery, but providing that the vulvar wounds are well healed there is no reason why a vaginal delivery should not be attempted.

Future pregnancies. For the young patient who has been successfully treated for her carcinoma of the vulva there is no contraindication to future pregnancies. Indeed psychologically it is a great boost for the woman who has had to undergo such extensive surgery to realize her desires to have further pregnancies. The youngest patient in J.M.M.'s series has had two successful pregnancies following radical surgical treatment of her carcinoma.

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Sexual activity in girls under 16 years of age

S. L. BARRON

Summary. Data on pregnancy, abortion, sexually transmitted disease and cervical dysplasia in girls under the age of 16 years were collected from British and American publications. Over half the pregnancies in girls under 16 ended in induced abortion, and those that continued had increased maternal and perinatal mortality, partly due to failure to attend for care. A prospective study in young teenagers found a high rate of fetal loss in pregnancies that followed abortions. Apart from an increased risk of cervical injury, abortion in girls under 20 carried the same risk of complications as for the American population as a whole. The risk of developing carcinoma of the cervix was doubled in women who began sexual activity before the age of 17 and a large survey found that 1·9% of the girls aged between 15 and 19 years had abnormal cervical cytology. Discouraging sexual activity before the age of consent seems to have a medical as well as a moral basis.

The legal dispute between Mrs Gillick and the West Norfolk Health Authority raises serious issues for all doctors who may be faced with having to advise a very young, sexually active girl. Although the House of Lords decided by a majority of 3 to 2 for the Health Authority, Lord Fraser made it clear that prescribing contraception for girls under 16, with or without parental consent, should not be done without a very good reason whilst Lord Brandon, in a dissenting judgment, considered the practice to be unlawful (*The Times* 1985).

Many doctors feel strongly that they have a duty to provide contraception for young girls who are already sexually active, in the hope of preventing unwanted pregnancies — with all that that implies. They assert that most of the youngsters who come for advice without their parents' knowledge would not seek advice at all if they thought that their parents would get to know.

The alternative view is that sexual activity below the age of 16 is potentially harmful, as well as being unlawful, and that doctors should be less permissive in their attitudes to young people. By offering contraception to girls under 16, doctors are condoning immorality and failing to point out the harmful medical effects of early sexual activity. In this context, early sexual activity should be regarded in the same way as smoking and drinking.

Whilst there is a wealth of literature about 'teenage pregnancy', most of it is concerned with women under the age of 20 and there are very few medical data specifically about girls under the age of 16.

The age of consent

Each country has its own legal restraint on sexual activity and the legal age of marriage varies from 12 in India to 18 in the Republic of China. In the United Kingdom, marriage is unlawful before 16, and parental consent is needed between the ages of 16 and 18. It is also a criminal offence for a man to have intercourse with a girl below the age of 16, although the girl herself does not commit a crime. It follows that intercourse below the age of 16 occurs in a context of social and legal disapproval, and that the prob-

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lem of sexual activity in young girls is more than a function of chronological age. The proportion of pregnancies which ended in abortion declined from 60% below the age of 14 to 36% in single girls aged 17–18. Above the age of consent, however, where conception occurred within marriage, the proportion ending in abortion was very low indeed (Table 1).

Throughout the world, improved standards of living and of education have resulted in a rise in the age of marriage whilst the age of menarche is falling. The gap between sexual and social adulthood is increasing (Hunt 1976) and it seems almost inevitable that teenage sexual activity outside marriage will increase.

The immediate effects of early sexual activity

Early sexual activity tends to occur in the context of what Schofield (1965) called the teenager behaviour syndrome which will be familiar to all gynaecologists: leaving home, promiscuity, pregnancy, sexually transmitted disease and suicide attempts. Pregnancy in such a context causes great distress and a high proportion of conceptions in girls under 16 end in legal abortion. Furthermore because such pregnancies go unrecognized for a time, abortion is often necessary in the second trimester (Table 2).

Induced abortion

A pregnancy conceived at the age of 15 could end in abortion a few weeks later, or in a registered birth at the age of 16. The OPCS has taken account of this and publishes statistics on pregnancy by the age at conception (OPCS 1985). The absolute number of pregnancies in girls under 15 years of age is small and the fluctuations over the past 10 years are not significant. When expressed as a rate per 1000 girls aged under 16, however, there appears to have been a small fall from 1976 to 1980 followed by what may turn out to be a significant rise, especially in the 15-year-old girls (Table 3).

The proportion of conceptions in 14-year-old girls which ended in legal abortion in 1982 was 60% and for all girls under 16 years of age it was 57·6%. Similar statistics are not available for Scotland, but Table 4 shows the percentage of pregnancies in girls under 16 which ended in abortion and the trends are similar to those for England and Wales. Compared with the population as a whole, abortions in girls under 16 were more likely to have been performed within the NHS and to have been done after 13 weeks gestation (Table 2). The need for late abortion is reflected in the methods used and prostaglandins were employed twice as often in girls under 16 as in the total population (Table 5).

The mortality ratio for abortion in women under 20 was lower than in any of the other age groups, and serious complications occurred no more frequently in those under 20 than in the remainder of the American population (Cates *et al.* 1983). One complication, cervical injury, was significantly higher in the younger age groups (Table 6) and the problem of the immature cervix which resists dilatation has been reported by Russell (1982) in his study of teenage pregnancy.

Late consequences of teenage abortion

It is exceedingly difficult to separate the effects of abortion from the effects of the associated social variables, but the WHO collaborative study (WHO Task Force 1979) concluded that the pregnancies which followed an induced abortion had an increased risk of low birthweight, which was related to the degree of dilatation of the cervix at the time of abortion. No conclusions were possible in relation to very young girls, because of the retrospective nature of the study. Russell (1982), however, was able to study in detail the later reproductive history of 167 girls under 16 whose first pregnancy was terminated. Of the 133 subsequent pregnancies, 19 were terminated and 24 (18%) aborted spontaneously; the remaining 90 pregnancies, which continued beyond 28 weeks, had a perinatal mortality rate of 55 per 1000. There were also 68 girls whose first pregnancies continued and 53 had a second pregnancy with a spontaneous abortion rate of 4% and a perinatal mortality rate of 22 per 1000. On this evidence, those who underwent abortion did far less well than those who continued with their pregnancy, but the groups were not really comparable in their social or emotional background.

Continuing pregnancy

As a result of legal abortion, there has been a marked fall in the proportion of pregnancies in the very young which go on to a registrable birth. Maternal deaths before the age of 16 are now, fortunately, rare and the most recent maternal mortality figures are available only for girls

Table 1. Proportion of teenage conceptions ending in legal abortion by age at conception (England and Wales, 1979–1983)

Age at conception (years)	Proportion ending in abortion (%)	
	Unmarried	Married
Under 14	60	—
14–	60	—
15–	54	—
16–	45	0
17–	38	4
18–	36	3
19–	36	3

Source: Birth statistics for 1984, series FM1 no. 11. (OPCS 1985).

Table 2. Abortion in girls under 16; proportion of those in the NHS and those performed after 13 weeks gestation (residents of England and Wales, 1979–1983)

	Girls under 16		All ages	
Abortions in England and Wales	18 654		634 243	
Number in NHS	12 488	(66·9%)	302 243	(46·7%)
Number over 13 weeks	4888	(26·2%)	98 568	(15·5%)

Source: OPCS, Abortion Reports; series AB, nos. 6–10.

Table 3. Conception rates in girls under 16 years of age

Year	Age at conception (years)			All <16 years	
	<14	14	15	Rate	% aborted
1974	1·0	5·3	19·7	8·6	48·6
1975	1·1	5·1	19·1	8·2	52·4
1976	1·0	5·0	18·3	7·9	53·4
1977	0·9	4·9	17·4	7·6	53·3
1978	1·1	4·6	17·5	7·6	51·8
1979	1·0	4·8	16·9	7·6	55·4
1980	0·9	4·4	16·2	7·2	54·3
1981	1·1	4·6	15·7	7·3	57·2
1982	1·1	4·9	17·0	7·8	57·6
1983	1·0	5·4	18·2	8·3	56·9

Rates are expressed as conceptions per 1000 girls at each age.
'<16' as rate per 1000 unmarried women aged 13–15.
'<14' as rate per 1000 unmarried women aged 13.
Source: Birth stastistics for 1984; series FM1, no. 11. (OPCS 1985).

under 20, who have very favourable rates (Table 7). The earlier figures for 1973–1975, however, showed that girls under 16 had a maternal mortality of 207 compared with 124 per million maternities in the age group 16–19, suggesting that those under 16 were at special risk. In a recent report from Nigeria, where mortality is still high, Harrison *et al.* (1985) reported that the maternal mortality rate in girls under the age of 15 was over three times the overall rate (Table 7).

Reports on the complications of pregnancy in very young girls are contradictory and difficult to interpret because of the coincidence of youth with social deprivation and poor attendance for antenatal care. The increased incidence of preg-

Table 4. Pregnancies in girls under 16, in Scotland

Year	Total births	Notified abortions	Percentage of pregnancies aborted
1974	150	208	58·1
1975	146	211	59·1
1976	140	218	60·9
1977	99	216	68·6
1978	106	202	65·6
1979	140	175	55·6
1980	113	233	67·3
1981	92	202	68·7
1982	121	245	66·9
1983	128	237	64·9

Source: Registrar General for Scotland (courtesy of Dr S. Cole).

Table 5. Method of abortion in girls under 16, compared with all ages. (Residents of England and Wales, 1979–1983)

	All ages		Under 16	
Method	*n*	%	*n*	%
Hysterotomy	2821	0·4	72	0·4
Hysterectomy	851	0·1	1	0·0
Vacuum aspiration only	480 897	75·8	13 110	70·3
Vacuum aspiration with D&C	77 574	12·2	1340	7·2
D&C or dilatation and evacuation	108	0·1	717	3·8
Other surgical methods	87	0·1	3	0·0
Prostaglandins only	24 057	3·8	1743	9·3
Prostaglandins with others	16 588	2·6	1129	6·1
Others	4093	0·6	277	1·5
Unknown	26 971	4·3	262	1·4
Total	634 047	100·0	18 654	100·0

D&C, Dilatation and curettage.
Source: OPCS, Abortion Reports for 1979–1983; series AB.

nancy-induced hypertension, however, is a consistent finding and one American study has shown it to be true after allowance was made for socio-economic factors (Duenhoelter *et al.* 1975). The other problem which is much discussed is the incidence of cephalopelvic disproportion due to incomplete growth of the pelvis and this seems to be related more to the 'menstrual age' (the time since menarche) than to chronological age. There is no evidence of an increased need for caesarean section (Sherline 1984).

The perinatal mortality rate in 1983 for mothers under 16 years of age was 26·9/1000, compared with an overall rate of 10·4/1000 (Table 8); nor does the disadvantage stop there, for the infant death rate in these mothers is 20 per 1000 births, exactly twice the overall infant death rate. In developing countries it is recognized that very early childbearing, even within marriage, leads to a high infant mortality (Hunt 1976). One important contribution to the high perinatal loss is the frequency of low-birthweight infants in mothers under the age of 16, even when allowance is made for the effect of socio-economic factors (Zlatnik & Burmeister 1977).

It has been suggested that the risk of fetal chromosomal abnormality is increased in young girls under the age of 20 (Hook 1984), but there is surprisingly little published information to support this view.

Sexually transmitted diseases

Attendances at clinics for sexually transmitted

Table 6. Mortality and morbidity associated with suction-curettage abortion at ≤12 weeks gestation by maternal age, 1975–1978

	Maternal age (years)					
	<17	18–19	20–24	25–29	30+	All ages
Mortality ratio (per 100 000)	1·3		2·1	2·0	2·9	1·9
Serious complications (per 1000)	0·8	1·5	2·0	2·1	1·5	n/a
Cervical injury (per 1000)	5·5*	3·3	3·1	2·6	1·7	n/a

* Differences highly significant; $P<0·001$.
n/a, Not available.
Source: Joint Program for Study of Abortion (JPSA) Study, USA. Cates *et al.* (1983).

Table 7. Maternal mortality rates by age (per million maternities)

	Age (years)	Maternal deaths (per 10^6)
England and Wales 1976–1978	Under 20	106
	20–24	70
	25–29	130
	30–34	145
	35–39	276
	40–44	975
	45+	3333
	All ages	130
Source: DHSS (1982).		
Zaria, Nigeria	<15	27 000
	15–	31 000
	16–	8000
	17–19	7000
	20–24	4000
	25–29	5000
	30+	11 000
Source: Harrison *et al.* (1985).		

Table 8. Outcome of viable pregnancies by maternal age

	Maternal age (years)						
Outcome	<16	16–19	20–24	25–29	30–34	35+	All ages
Stillbirth rate	13·4	7·1	5·4	5·1	5·7	8·2	5·7
Perinatal mortality*	26·9	13·4	10·1	9·3	9·8	13·8	10·4
Neonatal death rate†	15·2	7·8	5·9	5·2	5·2	7·1	5·8
Infant death rate†	20·0	15·1	10·9	8·6	8·4	10·4	10·0

* Per 1000 live and still births.
† Per 1000 live births.
Source: Infant and perinatal mortality, 1983. DH3 85/2 (OPCS 1985).

diseases have risen sharply in Britain and the USA over the past 20 years. Among the possible explanations for the rise are the increase in sexual activity among the young, the decreased popularity of the condom and the increased recognition of infections due to herpes and papilloma wart viruses. The rising prevalence of sexually transmitted viral infections is of special significance because of their suspected role in the genesis of cervical neoplasia.

Information on the incidence of sexually transmitted diseases in the very young is available only for the notifiable diseases of syphilis and gonorrhoea (DHSS 1984). The incidence of gonorrhoea in females under 16 for successive years showed an unsustained fall in 1979, but no consistent trend. The rates per 100 000 population were 6·44 in 1978; 3·62 in 1979; 5·99 in 1980; 5·30 in 1981 and 6·40 in 1982.

Carcinoma of the cervix

The two factors which have been repeatedly impugned as the cause of cervical cancer are sexual activity before the age of 17 and a history of more than one sexual partner (Rotkin 1973). Such a history increased the risk of developing severe dysplasia or invasive cancer by between 1·5 and 2 times. The theoretical reason for these findings, expounded by Coppleson (1969), is that the adolescent cervical epithelium is particularly susceptible to the oncogenic effects of the herpes hominis type 2 virus (HSV 2). More recent work suggests that the wart papilloma virus may be the causal agent (Singer & McCance 1985).

The peak age incidence of pre-invasive carcinoma of the cervix is between 30 and 35 but there is increasing evidence that dysplasia of the cervix occurs in young adolescents, Sadeghi *et al.* (1984) reported the results of a screening programme in the USA involving 796 337 cervical smears; in the age group 15–19 years, 18·8 per 1000 smears had abnormal cytology although only about 1 per 1000 had CIN 3 (Fig. 1), but none had invasive cancer. Jones *et al.* (1984), also from USA, reported the results of examining 1381 patients with an abnormal smear, 22% of whom were below the age of 20. In 97% of girls under 20 the lesion was on the ecto-cervix and easily treated.

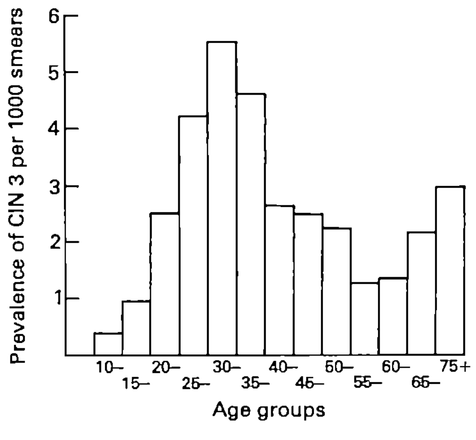

Fig. 1. Age-specific rates of cervical intraepithelial neoplasia grade 3 (CIN 3) per 1000 women screened in the United States in 1981. (Data from Sadeghi *et al* 1984).

Conclusions

There is no evidence of a dramatic increase in the incidence of induced abortion or sexually transmitted diseases over the past decade, but there are suggestions that the conception rate in girls under 16 may be rising. Although not a strictly medical matter, doctors are very aware of the sociological harm resulting from sexual activity before the age of 16 with the resultant disruption of schooling and of family life.

Early sexual activity, especially with more than one partner, increases the risk of developing carcinoma of the cervix and of pelvic infection with resultant infertility. Discouraging the young from extra-marital coitus is a moral issue and doctors are unwilling to act as moralists, particularly where this might conflict with advice affecting the welfare of their patients. Certainly neither the law nor the church has had much success in the matter. It looks as if early sexual activity is going to join smoking, drinking alcohol, the taking of drugs and eating too much animal fat, in the list of things that can damage health.

This paper is based on a report prepared at the request of the Scientific Advisory Committee of the RCOG. The views expressed are those of the author and do not represent a statement by the RCOG.

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Obstetric hysterectomy—an 11-year experience

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Summary. A total of 31 women had obstetric hysterectomy at St Mary's Hospital, Manchester, between 1972 and 1982. Elective caesarean hysterectomy was performed on nine occasions mainly because of pre-existing gynaecological problems such as fibroids or menorrhagia. Emergency hysterectomy most frequently followed uterine rupture, postpartum bleeding and major degrees of placenta praevia. The majority of patients required blood transfusion but postoperative problems were few. Late complications included infected discharge and cyclical bleeding after subtotal hysterectomy. There was one neonatal death but no maternal deaths. Although the operation is usually straightforward, and no major technical problems, such as urinary tract injury occurred, the decision to perform it as an emergency must be made before the patient's condition is extreme; the availability of senior staff is important.

Originally the operation of obstetric hysterectomy was performed because of life-threatening sepsis after prolonged labour, but by the 1950s was being undertaken for such minor indications as sterilization and fell into disrepute. The early history is reviewed by Durfee (1969).

Today, indication for the operation has somewhat changed; it does not always follow immediately after caesarean section, and may be necessary several hours after apparently uneventful vaginal delivery. This study reviews the results of 11 years' experience of obstetric hysterectomy at St Mary's Hospital, Manchester, and discusses its place in modern obstetric practice.

Subjects and methods

The hospital records of all 31 women who underwent this operation between 1972 and 1982 inclusive were examined and divided by the main indication for operation into an elective group (Table 1), and five categories of emergency obstetric hysterectomy (Table 2). The final decision to perform the operation in the emergency group was sometimes influenced by additional factors such as fibroids. There was only one neonatal death (extremely low birthweight) and no maternal deaths. In the 11 years studied, 48 110 babies were born at St Mary's Hospital, Manchester, giving a prevalence for obstetric hysterectomy of 1 in 1552 deliveries. The average age was 32 (range 23–43 years) and parity ranged from 1 to 6 (mean 2·4).

Indications for emergency obstetric hysterectomy

Ruptured uterus. All seven patients were parous (range 1–4; mean 2·4). One caesarean section was performed for fetal distress, and the other during violent spontaneous labour in a patient with two previous caesarean sections. Of the five patients delivered vaginally, four had labour induced near term, and there were four normal deliveries with one Kielland's rotational forceps delivery. These five patients all suffered major primary postpartum haemorrhage with well con-

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Table 1. Details of nine patients having elective caesarean hysterectomies

Patient no.	Age (years)	Parity	Previous CS	Indication	Operation	No. of units transfused
1	39	1+0	1	Fibroids, wanted TL	LSCS; subtotal hysterectomy	2
2	43	0+1	—	Fibroids, age	LSCS; subtotal hysterectomy	2
3	39	1+3	1	Fibroids	LSCS, total hysterectomy; LSO	2
4	38	1+0	1	Fibroids, wanted TL	LSCS; subtotal hysterectomy; LSO	4
5	38	3+0	—	Fibroids	Classical CS; subtotal hysterectomy	2
6	38	4+0	3	Fibroids	LSCS, total hysterectomy	4
7	37	2+0	—	Previous menorrhagia	LSCS, total hysterectomy	4
8	33	2+0	2	Previous menorrhagia, wanted TL	LSCS; total hysterectomy	—
9	36	3+2	3	Wanted TL	LSCS; total hysterectomy	—

CS, Caesarean section; TL, tubal ligation; LSCS, lower segment caesarean section; LSO, left salpingo oophorectomy.

Wanted TL indicates previously stated wish to be sterilized after current pregnancy.

Table 2. Indication and mode of delivery for 22 emergency obstetric hysterectomies

		Mode of delivery			Type of hysterectomy	
Major indication	*n*	SVD	Forceps	CS	Subtotal	Total
Ruptured uterus	7	4	1	2	4	3
PPH	6	4	2	0	4	2
Major placenta praevia	5	—	—	5	2	3
Bleeding at CS	2	—	—	2	1	1
Non-obstetric	2	—	—	2	1	1

SVD, Spontaneous vaginal delivery; CS, caesarean section, PPH, primary postpartum haemorrhage.

tracted uteri leading to laparotomy 1–4 h later. One patient in this group also sustained a ruptured bladder after normal delivery.

Primary postpartum haemorrhage. All six patients were parous (range 1–5; mean 2·8); four began labour spontaneously at term, and only one of this group required forceps delivery. Two patients had labour induced, one for hypertension and the other for prolonged pregnancy. Two patients had uterine hypotonia, three had manual removal of placentas which were described as adherent and the sixth had a normal third stage but continued to bleed after removal of adherent placental fragments under general anaesthesia. Each patient needed a laparotomy for persistent uterine bleeding; blood transfusions ranged between 5 and 18 units.

Major placenta praevia. All five patients were parous (range 1–6; mean 3·6). In each the placenta was known to be anterior (by ultrasound scan) and four had had a previous caesarean section (range 1–3; mean 1·75). Caesarean section was planned for each patient but four had emergency operations because of sudden heavy bleeding. The hysterectomies were necessary to halt persistent bleeding from the area of the old uterine scar. Blood transfusion varied between 3 and 12 units (mean 7·4).

Bleeding at caesarean section. One patient had had a uterine rupture during a mid-trimester termination of pregnancy. She was subsequently delivered normally but in the index pregnancy caesarean section was performed after failed induction of labour and placental fragments were adherent to the uterine scar resulting in heavy bleeding. The other patient (para 5+3) bled heavily at 24 weeks and had a classical caesarean section at 26 weeks; unstoppable bleeding led to hysterectomy. The baby weighed 820 g and died shortly after birth.

Non-obstetric indications. Both patients were known to have cervical fibroids and required emergency caesarean section because of cord prolapse in one and obstructed delivery in the other. Hysterectomy was performed because the fibroids were considered likely to necessitate this management ultimately and because the patients were requesting sterilization.

Complications

Table 3 shows that complications were few in this series and can be divided into operative, early and late. Almost all patients were anaemic post-operatively but very few required blood transfusion once they had recovered from the immediate operation. A course of iron therapy was sufficient in all but four patients. Mean hospital stay was 10·2 days (range 4–17 days). Nine patients failed to attend for postnatal follow-up. Cervical discharge and cyclical bleeding were severe enough to require excision of the cervical stump in one patient, but in two patients cautery to the cervical canal sufficed.

Table 3. Complications associated with 31 obstetric hysterectomies

	Type of hysterectomy	
Complication	Subtotal	Total
Operative		
Bleeding from adnexae necessitating salpingo-oophorectomy	2	0
Early		
Wound infection	2	1
Pyrexia	2	1
Chest infection	1	2
Urinary infection	0	2
Depression	1	1
Late		
Cervical discharge	5	1*
Cyclical bleeding	2	0
Pain from adherent ovaries	1	0
Cervical remnant after 'total' hysterectomy	—	3

* Cervical remnant despite intended total hysterectomy.

Discussion

This series of 31 obstetric hysterectomies with low morbidity and no mortality contrasts with previous series (Brenner *et al.* 1970) and suggests that the place of the operation might be reconsidered, after many years being out of favour. Similarly, emergency procedures are associated with far greater problems than the elective operation: 52% as against 10% in one series (Barclay 1970). The same can be seen in the case of maternal mortality. It is possible that delay in making a decision concerning operation is a major factor.

In the present series the procedure was performed almost twice as often, and in women of lower parity, as in the series of emergency obstetric hysterectomies described by Smith (1982) (1 in 1552 *vs* 1 in 2905 deliveries). The lower threshold (for the emergency operation especially) perhaps explains the lower morbidity and no mortality, the operation being performed well before the patient's condition was desperate. A high frequency of previous caesarean section (52%) is also noted by other authors: 26% by Giwa-Osagie *et al.* (1983), and 72% by Barclay (1970). This seems especially to be the case if an anterior placenta praevia is present. Subtotal hysterectomy is not to be scorned and may, in fact, have less mortality in critical situations (Giwa-Osagie *et al.* 1983). Although the present series has an almost even distribution of subtotal and total procedures, the trend has been to prefer total hysterectomy which is quite straightforward if the patient's condition is good: the rule when an early decision has been taken.

Several factors, such as safety of modern anaesthesia and blood transfusion, have led to a much greater willingness to perform elective caesarean hysterectomy primarily because of fibroids, thus avoiding the need for two operations. It was much less common in Barclay's series (1970) at 6·4%, but has been accepted as a valid indication by Park & Duff (1980).

Uterine rupture provides a strong indication for obstetric hysterectomy whether or not caesarean section has been performed. The danger of oxytocin infusions in grand multipara with epidural blocks is clear (Smith 1982), and less than skilful use of Kielland's forceps can be catastrophic. Extension of tears into adjacent structures such as the bladder, as occurred here, emphasizes the observation by Smith (1982) that the obstetrician must be prepared for all eventualities in this situation. The place of primary surgical repair of the tear seems small. The desire to have more children is understandable after a first labour, but here uterine rupture is almost unknown unless caused by unskilled use of forceps (O'Driscoll & Meagher 1980). In a multiparous patient this wish should rarely argue in favour of surgical repair; the scar can only be of suspect integrity and may rupture before labour in a subsequent pregnancy. If circumstances dictate primary surgical repair, an effective sterilization procedure should be seriously considered, due regard being given to the failure rate of sterilization at caesarean section: over 3% after a Pomeroy procedure (Pletsch & Sandberg 1963). Although suture of a dehisced caesarean scar is acceptable, these cases should not really be regarded as having a ruptured uterus.

Barclay (1970), Smith (1982) and Giwa-Osagie *et al.* (1983) have all noted the dangerous combination of placenta praevia and previous caesarean section. In the present series four out of five patients with anterior praevia had a previous caesarean section. An anterior praevia becomes morbidly adherent to the uterine scar and produces a degree of placenta accreta, Kistner & Friesen (1968) found that at least 20% of placenta accreta occur in association with previous caesarean section. A caesarean section in these circumstances becomes especially difficult as the placental site bleeds very freely. An early decision is essential to avoid shock and coagulopathy (DHSS 1982; Smith 1982). The patient must be warned of the high probability.

The two patients who had hysterectomy because of unstoppable bleeding at caesarean section are grouped separately as they appear to belong to a discrete but identifiable group. One patient had a uterine scar due to a tear produced at termination of pregnancy years previously, and the placenta was adherent. This problem is mentioned by Prevedourakis (1974). The other patient had placental adherence to an old classical section scar and continued bleeding which is a further complication of this operation.

Injury to bladder or ureter is entirely lacking in this series. Although this does not give rise to complacency it contrasts with rates of between 5·3% (Barclay 1970) and 7·4% (Haynes & Martin 1979). Smith (1982) experienced an unstated number of ureteral injuries in his 14 cases.

The other important operative complication concerns haemostasis. Oedematous tissues and adhesions from previous caesarean section make this predictable (Prevedourakis 1974) and progressive coagulopathy compounds the problem. Persistent bleeding from utero-ovarian vessels occurs in perhaps 10% (Barclay 1970), and may require sacrifice of an appendage; this should not be regarded a surgical failure. It should be remembered that continued intra-peritoneal bleeding was found at postmortem in each of the three maternal deaths in the small series of 14 reported by Smith (1982).

Problems with the cervical stump seem to be common: 11·4% of a total 866 reported by Barclay (1970). Troublesome discharge and cyclical bleeding is a major reason for performing total hysterectomy if at all possible. The possibility of leaving a small portion of cervix at supposed total operation is demonstrated here and also experienced by Smith (1982); it is no cause for concern but avoidance is discussed by Barclay (1970) and Brenner *et al.* (1970). No case of stump carcinoma was encountered in the large series of Pletsch & Sandberg (1963) or Barclay (1970) but regular cytology must be performed if the cervix is retained. Pain from adherent ovaries can be another late problem possibly needing oophorectomy but ignored by other authors.

The question arises as to alternative treatment avoiding hysterectomy which may be seen as too drastic. Vaginal or uterine packs have long been condemned (Waters 1952). Ligation of internal iliac arteries may daunt the less experienced. However, the pelvic blood supply is so abundant (Burchell 1968) that bleeding may merely be reduced. In a patient of low parity it is worth considering, together perhaps with ligation of the ovarian arteries, which contrary to expectations does not always produce ovarian atrophy (Le Cocq 1966). It is probably unwise in cases of uterine rupture or placenta accreta (Park & Duff 1980). Ligation of the uterine arteries themselves (not the veins) was advocated by Waters (1952). Radiologically controlled embolization of vessels has been advocated in pelvic bleeding by Brown *et al.* (1979) and Rosenthal *et al.* (1983), but it is clear that this procedure is really only possible in a small number of centres, and the waste of valuable time may be irretrievable.

Conclusions

The operation of obstetric hysterectomy is most valuable. The decision to perform it should be taken early and preferably by a senior obstetrician; in this way excellent results will be obtained Except in desperate circumstances total hysterectomy is preferred thus avoiding late sequelae involving the cervical stump. With an experienced surgeon, complications should be no greater than those found after either caesarean section or hysterectomy alone; good technique will minimize urinary tract injuries and haemorrhagic problems. Ligation of internal iliac arteries may be considered in patients of low parity.

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Interval from rupture of the membranes to delivery and neonatal respiratory adaptation

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Summary. The influence of the time interval from rupture of the membranes to delivery on neonatal respiratory adaptation was analysed in a prospective study of all infants born in Göteborg, Sweden in one year. The correlation between the incidence of respiratory disorders and the rupture-delivery interval was analysed in all preterm infants ($\leqslant 36$ weeks, $n = 240$) and in all term infants born by caesarean section ($n = 452$). A uniform pattern was found for all preterm infants, irrespective of mode of delivery, and for the term infants born by caesarean section. The curve was 'U-shaped' with higher incidence of respiratory diseases in infants born immediately after rupture of the membranes than in those born 3–36 h after membrane rupture. The incidence increased again in infants born >36 h after membrane rupture. The same pattern was found for all kinds of respiratory diseases including idiopatic respiratory distress syndrome. Therefore, there seems to be no advantage in postponing delivery >36 h after rupture of the membranes.

The effects of prolonged rupture of the membranes on the risk of developing neonatal respiratory diseases has been debated for more than 10 years. Several studies have reported a decreased incidence of respiratory diseases in conjunction with prolonged rupture of the membranes (Thibeault & Emmanouilides 1977; Miller *et al.* 1978; Yeung 1982; Curet *et al.* 1984) and other studies have failed to show such a protective effect (Jones *et al.* 1975; Christensen *et al.* 1976; Papageorgiou *et al.* 1981; Perkins 1982). Differences in the criteria used to select the study population and variations in the definition of the respiratory diagnoses used may all have contributed to the conflicting findings.

Less interest has addressed the question whether differences in the rupture-delivery interval, within the normal range, have an impact on the process of neonatal pulmonary adaptation, and whether a particular interval provides the optimal conditions for neonatal lung performance.

We have investigated this question in a prospective study in an unselected population of all infants born in one year in Göteborg, Sweden.

Patients and methods

Since virtually all infants in Goteborg are born in one of the two maternity hospitals it was possible to obtain an unselected population. The general standard, equipment, treatment principles and neonatal care are similar in both hospitals. This study was part of an extensive prospective study of all newborns with neonatal respiratory diseases in a total population.

Over a 12-month period all live-born infants in

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Göteborg were screened for signs of respiratory distress (breathing frequency >60/min, grunting, cyanosis or chest wall retraction) during the first 5 days of life. These infants were referred to a neonatal unit.

In addition all infants born by caesarean section, all infants <37 weeks or <2500 g and all those with Apgar scores of ≤6 were referred to the neonatal unit.

Respiratory disturbance (RD) was diagnosed in all those infants who fulfilled any of the following criteria: breathing frequency of ≥60 breaths/min for ≥3 h, 'grunting' or chest wall retractions at 2 h of age, or central cyanosis. Idiopathic respiratory distress syndrome (IRDS, or hyaline membrane disease) was diagnosed if chest films showed a reticulogranular pattern, the calculated right to left shunt increased over the first 24 h, and blood cultures were negative.

Assessment of gestational age was based on the number of complete weeks from the onset of the last menstrual period, from ultrasound examination early in pregnancy and from clinical paediatric assessment as described by Finnstrom (1977).

Information concerning past obstetric history, current pregnancy and events during delivery was collected for all these patients.

The time of rupture of membranes was determined on the basis of the history given by the patient and, when necessary, the diagnosis was confirmed by a fern test or the pH reaction of the vaginal fluid. The interval from membrane rupture to delivery was calculated in hours.

Preterm labour was often postponed with betamimetics. After labour had been tocographically confirmed, and provided the cervical dilatation was ≤5 cm, terbutaline was given, initially intravenously and then orally, until week 36. Terbutaline was also used if the membranes had ruptured. Antenatal treatment with corticosteroids was not routine at the department.

Statistical analyses used the χ^2 test.

Results

Figures 1 and 2 show the relation between the incidence rate of all respiratory disturbances and the rupture-delivery interval. In preterm newborns (≤36 weeks) the incidence of RD was significantly higher in the infants born immediately after membrane rupture than in those born 3–36 h after rupture. When the rupture-delivery interval was >36 h the rate of RD again increased significantly (i.e. the curve is U-shaped) (Fig. 1). This pattern persisted when

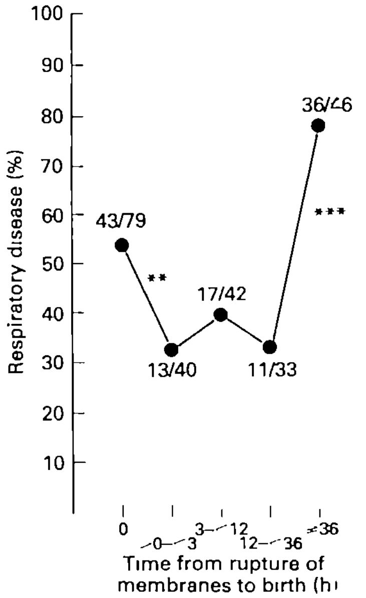

Fig. 1. Incidence of respiratory disease in 240 preterm infants (≤36 weeks) at different rupture-delivery intervals. $^{**}P<0{\cdot}01$, $^{***}P<0{\cdot}001$.

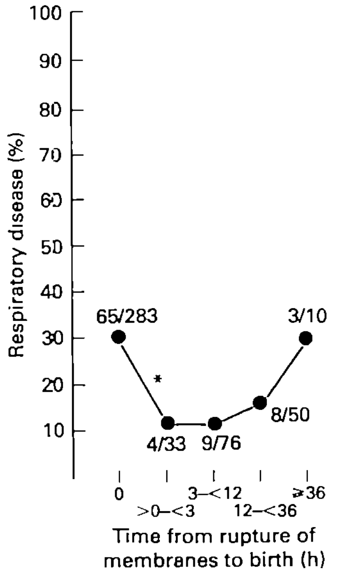

Fig. 2. Incidence of respiratory disease in 452 full term infants (≥37 weeks) born by caesarean section at different rupture-delivery intervals. $^{*}P<0{\cdot}05$

the groups were subdivided into vaginal and caesarean births (Table 1).

The same pattern was also found in the term infants (≥37 weeks gestation) born by caesarean section (Fig. 2). The rate of RD was significantly lower in the infants born 3–12 h after membrane rupture than in those born immediately after rupture. The incidence of RD increased again in infants born >36 h after membrane rupture, but there were only few babies in this group and the difference was not statistically significant.

This study did not provide an estimate of the risk of RD in relation to rupture-delivery intervals in infants born vaginally at full term, but in this group the overall incidence of RD is very low (Hjalmarson 1981).

There was no difference in the rate of treatment with betamimetics between healthy infants and those with RD. In general, 60–70% of all the women delivered at <33 weeks and about 30% of those delivered between 33 and 36 weeks had received betamimetic treatment.

The U-shaped pattern was also found when the rate of IRDS was analysed in preterm infants (Table 2). IRDS occurred in 14 of the 79 (18%) infants born immediately after membrane rupture and in 2 of 115 (2%) born between 0·1 and 36 h after membrane rupture, the difference is statistically significant ($P<0{\cdot}001$). In infants born >36 h after rupture the incidence rate of IRDS was again significantly increased to 15% (7 of 46) ($P<0{\cdot}01$). The pattern persisted when the infants ≤32 weeks gestational age were analysed separately. The incidence rates were 7/17 (41%), 2/12 (17%) and 6/18 (33%) respectively in infants born 0 h, 0·1–<36 h and ≥36 h after membrane rupture, but the differences were not statistically significant.

Table 1. Incidence rates of respiratory diseases (RD) at different rupture-delivery intervals in preterm infants (≤36 weeks), related to mode of delivery

	Rate of RD			
	Vaginal deliveries		Caesarean section	
Rupture-delivery interval (h)	(*n* = 164)	%	(*n* = 76)	%
0	12/25	48	31/54	57†
0–<3	13/36	36	0/4	0
3–<12	16/39	41	1/3	33†
12–<36	8/27	30*	3/6	50
≥36	30/37	81*	6/9	67

Values denoted by * and †, respectively, differed significantly ($P<0{\cdot}05$)

There were only 13 infants with RD due to infections and no correlation between the rupture-delivery interval and RD could be demonstrated in this small group.

Discussion

The purpose of this study was to investigate whether, and if so how, the interval from rupture of membranes to delivery influences pulmonary adaptation at birth. Previous studies have addressed the potential advantage of a long interval from rupture to delivery, which may lead to endogenous cortisol and/or catecholamine production and hence to a decreased risk of respiratory disorders, primarily IRDS (Richardson *et al.* 1974). This theory has been questioned and other studies have not correlated the beneficial effect of prolonged membrane rupture, to the risk of IRDS (Jones *et al.* 1975). In our study the incidence rate of RD was related to the rupture-delivery interval, and the most striking finding was that this correlation was not linear. Instead, the resultant curve showed a high incidence rate of RD in conjunction with a short rupture-delivery interval, the risk of RD decreased and remained low in infants born 3–36 h after membrane rupture but increased again beyond 36 h. This pattern was found in all preterm infants and in term infants born by caesarean section. The higher incidence of RD when delivery occurred immediately after membrane rupture was not explained by a high rate of emergency caesarean sections, and depressed infants. In fact more than 90% of these sections were performed before the onset of labour, and low Apgar scores were not more frequent in this group.

Fedrick & Butler (1972) reported an increased risk of IRDS after caesarean sections performed before membrane rupture and the onset of labour. Our results confirm these findings, moreover, we found that the increased risk was not limited to IRDS but generally affected the respiratory adaptation in newborn infants. We also found that the rate of IRDS increased again in infants born >36 h after membrane rupture.

Experiments have demonstrated that animals born by caesarean section without prior labour had more lung water than those born after the onset of labour (Bland *et al.* 1979). The likely

Table 2. Incidence rates of hyaline membrane disease (IRDS) in preterm infants (≤36 weeks) at different rupture-delivery intervals, related to mode of delivery

Rupture-delivery interval (h)	Rate of IRDS					
	All		Vaginal delivery		Caesarean section	
	n	(%)	*n*	(%)	*n*	(%)
0	14/79	(17·7)	4/25	(16)	10/54	(18·5)
0·1–<36	2/115	(1·7)	2/102	(1 9)	0/13	(—)
≥36	7/46	(15·2)	6/37	(16.2)	1/9	(11·1)

The differences between IRDS rates for all infants between 0 and 0·1–<36 h, and 0 1–<36 h and ≥36 h, respectively, were significant ($P<0{\cdot}001$, $P<0\ 01$).

reason for this is lack of labour-induced production of catecholamines. These compounds have been shown to inhibit secretion and enhance absorption of lung fluid in term animals (Walters & Olver 1978). This mechanism might be responsible for the elevated risk of RD in the infants born immediately after membrane rupture.

The risk of RD was found to increase again with rupture-delivery intervals of >36 h. The reason for this is not clear. One explanation is suggested by the results of Whittle and colleagues (Whittle *et al.* 1977; Whittle & Hill 1980) who found an inverse relation between the lecithin/sphingomyelin (L/S) ratio and the length of labour after rupture of membranes. Short strong labours were found to increase the L/S ratio, whereas long labours decreased the L/S ratio. The changes in L/S ratio are probably not mediated by endogenous corticosteroids since cord serum corticosteroid levels were lowest in patients with rising L/S ratios during labour, and highest in the group in which the L/S ratio fell.

The danger of neonatal infections after a long rupture-delivery interval has evoked much consideration. It has been generally accepted that not all infections are secondary to an ascending infection through the cervix, but rather the result of a primary infection acquired *in utero* before membrane rupture. In fact, it has been suggested that the primary infection might be an aetiologic factor in premature membrane rupture. We found no evident correlation between a long rupture-delivery interval and increased incidence of pulmonary infections.

Finally, it was interesting to find that in the group of preterm infants that was analysed the mode of delivery did not appear to influence the relation between the rupture-delivery interval and the incidence of RD. This means that the effect of the rupture-delivery interval is not altered by factors such as vaginal squeeze in these infants.

In conclusion, the rupture-delivery interval has an obvious effect on neonatal respiratory adaptation with a correlation that is not linear but has a pattern showing high risk for RD in conjunction with delivery immediately after membrane rupture. The risk then decreases and is low with rupture-delivery intervals of 3–36 h after which the risk increases again. Thus there seems to be no advantage for neonatal lung function in postponing delivery more than 36 h after membrane rupture.

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Spontaneous early preterm labour associated with abnormal genital bacterial colonization

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Summary. The association between infection and preterm labour was studied in 72 women in spontaneous preterm labour between 26 and 34 weeks gestation and in 26 control subjects having an elective caesarean section at the same gestational age. The genital microbial flora of each group was studied comprehensively and included mycoplasmas, chlamydiae, ureaplasmas and anaerobes. Subsequent neonatal infection and chorioamnionitis was also studied. Abnormal bacterial colonization, the presence of ureaplasmas, heavy growth of mycoplasmas and chorioamnionitis were all found significantly more often in the study group. This supports the premise that a significant proportion of idiopathic preterm labour is associated with infection and this may permit better prediction and prevention of preterm birth. The continued use of tocolytics should depend upon the identification of the presence or absence of infection. Infection appeared to be the result rather than the cause of ruptured membranes. A recommendation with respect to the classification of abnormal or normal bacterial colonization between 26 and 34 weeks is suggested on the basis of strict criteria.

Preterm labour accounts for only 5–10% of all births but preterm birth is responsible for a disproportionately large percentage of perinatal deaths. Rush *et al.* (1976) reported that 85% of perinatal deaths not due to congenital abnormality occurred in infants with gestational ages between 22 and 37 weeks.

The aetiology of preterm labour is multifactorial (Turnbull & Anderson 1978) and infection is thought to be one of the factors. To investigate this, we have compared genital tract flora of women presenting in preterm labour between 26 and 34 weeks with that of women who were delivered at a similar gestational age but who were not in labour.

Patients and methods

One hundred women were investigated, consisting of a study group of 74 patients and a control group of 26 patients. The study group comprised women who presented in labour with or without ruptured membranes at between 26 and 33 completed weeks of pregnancy. Labour was diagnosed when there were regular, painful and palpable contractions of the uterus occurring

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with a frequency of at least two in 10 min. Ruptured membranes were diagnosed when there was a pool of amniotic fluid visible on vaginal speculum examination.

The control group comprised women who were not in labour but required abdominal delivery before 34 weeks gestation because of some fetal or maternal complications of pregnancy; all had intact membranes.

Two patients were later excluded from the analysis of the study group because their infants were born with lethal congenital abnormalities (tracheal atresia in one and renal agenesis in the other). Of the 72 remaining study patients, 28 (39%) had intact membranes and 44 (61%) had ruptured membranes at the start of preterm labour.

There was no difference between the study and control groups with respect to birthweight or gestational age at birth, gestational age at entry to the study, age, race or social class.

Methods

Informed consent was obtained from all patients and identical specimens were obtained from both study and control groups. Samples were collected for serology, haematology, microbiology (bacteria, viruses, yeasts, chlamydiae, mycoplasmas and ureaplasmas), and histopathology. Specimens from the study group were taken at the first vaginal examination after admission. Specimens from control patients were obtained during the 24 h before elective delivery. All the specimens, a summary of which is shown in Table 1, were collected by the same investigator (R.F.L.) and were examined without knowing whether the patient belonged to the study or control group

A total white cell count and a midstream specimen of urine were processed as part of the routine investigation of this type of hospital in-patient.

The endocervical smear was stained by Gram's method. The rectal swab was plated on neomycin blood agar, incubated at 37°C for 24 h and was then broken into enrichment medium which was incubated at 37°C overnight to culture β-haemolytic streptococci. The medium comprised nutrient broth, 4 μg/ml of gentamicin, 10 μg/ml of nalidixic acid, and 5% defibrinated horse serum. The endocervical swabs and high vaginal swabs were plated and the cultures incubated as shown in Table 2.

Bacteria were identified, at least to the genus level, according to the methods of Cowan & Steel (1974). Further identification was achieved by using commercially available systems in kit form. The three micro-organisms with the heaviest growth and the presence or absence of polymorphonuclear leucocytes (PMNL) were reported for both endocervical and high vaginal swabs.

Since there is normally a variety of organisms in the upper vagina, the following strict criteria were used in considering colonization to be abnormal or normal; these are summarized in Table 3

Group (a). Colonization with *Lactobacillus* sp.

Table 1. Specimens obtained from both study and control groups

Examination	Specimen
Bacteriology	High vaginal swab Endocervical swab Rectal swab Endocervical smear Midstream specimen of urine
Haematology (total white cell count)	Blood
Virology	Endocervical swab Serology
Mycoplasmas/ureaplasmas	High vaginal swab
Chlamydiae	Endocervical swab
Histopathology	Umbilical cord Villous plate Extraplacental membranes

Table 2. Procedure for examination of endocervical and high vaginal swabs

Medium	Atmosphere	Incubation time at 37°C (h)
Blood agar	Aerobic	48
Blood agar	Anaerobic*	72
Heated blood agar (chocolate)	Carbon dioxide**	48
MacConkey agar	Aerobic	48
Sabourauds agar	Aerobic	48
Thayer–Martin	Carbon dioxide**	48
Neomycin blood agar	Anaerobic*	72
Enrichment broth	Aerobic	24

*Anaerobic atmosphere—Oxoid anaerobic gas generating kit (Oxoid Ltd , Basingstoke, Hampshire, England).
**Carbon dioxide incubator with air plus 5–10% carbon dioxide

or diphtheroids was always considered normal irrespective of their concentration (colony counts/agar plate) or the presence of PMNL

Group (b). Colonization with *Escherichia coli*, *Bacteroides fragilis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae* and *Candida albicans*, at any concentration, was considered abnormal in the presence of PMNL but normal in the absence of PMNL.

Group (c). Colonization with other organisms found was considered to be abnormal only if they were isolated in large numbers (≥60 colonies/agar plate) in the presence of PMNL.

Specimens to be tested for chlamydiae,

Table 3. Classification of the presence of organisms as normal or abnormal

Micro-organisms	Growth (no of colonies/plate)	Presence of PMNL*	Classification
Group (a)			
Lactobacillus sp	≥20	±	Normal
Diphtheroids			
Group (b)			
Escherichia coli			
Bacteroides fragilis	≥20	+	Abnormal
Neisseria gonorrhoeae	≥20	–	Normal
Haemophilus influenzae			
Candida albicans			
Group (c)			
Klebsiella sp			
Staphylococcus epidermidis			
Bacteroides sp (excluding *B fragilis*)			
Proteus sp			
Micrococcus			
Veillonella sp			
Gardnerella vaginalis			
Haemophilus aegyptius			
Yeasts (excluding *Candida*)	≥20	+	Abnormal
Fusobacterium fusiforme	20–59	+	Normal
Streptococci	≥60	+	Abnormal
β-haemolytic			
non-haemolytic			
microaerophilic			
anaerobic			
S. faecalis			
S viridans			

*PMNL, Polymorphonuclear leucocytes

mycoplasmas and ureaplasmas were stored in transport medium in liquid nitrogen at −70°C and like the histopathological specimens were examined as a group at the end of the study.

Mycoplasma hominis and *Ureaplasma urealyticum* were identified with the method described by Taylor-Robinson and Furr (1981) and the numbers of organisms were expressed in colour-changing units (ccu). The isolation of *Chlamydia trachomatis* was undertaken by a modification of the method described by Thomas *et al.* (1977) using cyclo-heximide treated McCoy cells.

Viruses were sought using four cell lines: cynomologus monkey kidney cells, Hep-2 cells, Vero-cells and human embryonic lung cells (Hel cells).

From the specimens of cord, villous plate and extraplacental membranes fixed in formalin, smaller sections were taken for histopathological examination. A 3 cm transverse section of cord was taken, a cube measuring 1·5 cm^3 was removed from the fetal surface of the placenta and a 3 × 0·5 cm strip was cut from the membranes. Thereafter the blocking, staining and mounting of the specimens were identical and carried out by conventional methods.

Neonatal infection was diagnosed if neonatal blood cultures were positive or if in the first 48 h of life the signs of infection (respiratory distress, early jaundice, apnoea, neutropenia or elevated immature white cell count) were sufficient for the infant to receive a 5-day course of antibiotics.

Chorioamnionitis was diagnosed if there was histological evidence of PMNL infiltration into any of five areas of the cord, membranes or placenta. These five areas were (i) the cord vessels, (ii) the extraplacental membranes, (iii) the chorionic plate and the subchorial lake of the villous plate, (iv) the villi and (v) the intervillous space. Histological data were available from 64 patients, 43 in the study group and 21 in the control group.

Statistical significance of the data was calculated using either Students *t*-test or χ^2 test with Yates' correction for small numbers.

Results

The various organisms isolated and the relative frequency with which they appeared in the study and control groups are shown in Table 4.

Abnormal colonization as classified in Table 3 occurred in 34 (47%) of the study patients but in only four (15%) of the control patients ($P<0·01$).

U. urealyticum was isolated significantly more often from the study patients (80%) than from the control patients (46%) ($P<0·01$). *M. hominis* was isolated from 24% of the study patients and from 8% of the control patients though the difference did not reach statistical significance

Eighteen percent of the study group and none of the control group ($P<0·05$) were colonized by large numbers (>10^5 ccu) of *M. hominis*. *C. trachomatis* was isolated from five of the study group but from none of the control group.

Viral studies failed to show any positive findings. Viruses were not isolated from any of the endocervical swabs. Many of the cell cultures showed early disruption of cells characteristically due to heavy bacterial contamination despite antibiotics in the culture medium. No patient exhibited a significant change in the titre of viral antibodies.

Proven urinary tract infections were found in 6% of the study group and 4% of the control group. There was no significant difference between study and control groups with respect to mean total while cell count taken on admission in preterm labour or before elective caesarean sections. The mean total white cell count was 11·8 (SD 4·1) × 10^9/l in the study group and 11·0 (SD 3·9) × 10^9/l in the control group. The mean total white cell count on admission in preterm labour was 10·7 (SD 2·9) × 10^9/l in those patients who had evidence of abnormal bacterial colonization compared with 12·5 (SD 4·1) × 10^9/l in those found to have normal colonization.

Histological evidence of chorioamnionitis was found in 24 of 43 (56%) patients in the study group compared with only two of 21 (10%) in the control group ($P<0·002$).

In the study group, there was no significant increase in the incidence of abnormal bacterial colonization with respect to time since last coitus, although there was a high incidence of chorioamnionitis when coitus took place within 7 days before the study.

The carriage of *M. hominis* by patients in social classes I, II, and III combined was 18% compared with 54% by those in social classes IV, V and unclassified ($P<0·02$). The carriage of *C. trachomatis* followed a similar pattern, that is 4% compared with 30% respectively ($P<0·02$).

There was no significant difference between birthweight or gestational age at birth for those

Table 4. Frequency of isolation of micro-organisms from women in preterm labour (study group) and from control group

Micro-organisms	Study group ($n = 72$)	Control group ($n = 26$)	Total ($n = 98$)
Lactobacillus sp	43 (60%)	20 (77%)	63 (64%)
S epidermidis	21 (29%)	9 (35%)	30 (31%)
Bacteroides sp. (non-fragilis)	15 (21%)	1 (4%)	16 (16%)
Diphtheroids	6 (8%)	6 (23%)	12 (12%)
Microaerophilic streptococci	11 (15%)	1 (4%)	12 (12%)
Esch coli	6 (8%)	3 (12%)	9 (9%)
C albicans	8 (11%)	1 (4%)	9 (9%)
S viridans	7 (10%)	2 (8%)	9 (9%)
Non-haemolytic streptococci	6 (8%)	0 (0%)	6 (6%)
Proteus sp	1 (1%)	3 (12%)	4 (4%)
Bacteroides fragilis	4 (6%)	0 (0%)	4 (4%)
β-haemolytic streptococci			
Group B	4 (6%)	0 (0%)	4 (4%)
Others	4 (6%)	0 (0%)	4 (4%)
Anaerobic streptococci	3 (4%)	0 (0%)	3 (3%)
Veillonella sp.	2 (3%)	1 (4%)	3 (3%)
Klebsiella sp	2 (3%)	1 (4%)	3 (3%)
S faecalis	2 (3%)	1 (4%)	3 (3%)
G vaginalis	2 (3%)	0 (0%)	2 (2%)
N. gonorrhoeae	2 (3%)	0 (0%)	2 (2%)
Fusobacterium fusiforme	1 (1%)	0 (0%)	1 (1%)
H influenzae	1 (1%)	0 (0%)	1 (1%)
H aegyptius	1 (1%)	0 (0%)	1 (1%)
Yeast (non-candida)	1 (1%)	0 (0%)	1 (1%)
Micrococcus	1 (1%)	0 (0%)	1 (10%)
M hominis	17 (24%) ($n = 71$)	2 (8%)	19 (20%) ($n = 97$)
U. urealyticum	57 (80%) ($n = 71$)	12 (46%)	69 (71%) ($n = 97$)
C. trachomatis	5 (8%) ($n = 71$)	0 (0%)	5 (5%) ($n = 97$)

patients with or without colonization, neonatal infection or chorioamnionitis.

The incidence of abnormal bacterial (46%), mycoplasmal (25%), ureaplasmal (79%) and chlamydial (4%) colonization in patients with intact membranes was almost identical to that in patients with ruptured membranes. This suggests that abnormal colonization *per se* was not responsible for membrane rupture. Neonatal infection and chorioamnionitis were present in only 13% and 33% respectively of those patients who had intact membranes compared with 27% and 69%, respectively, of those who had ruptured membranes. This suggests that infection developed as a consequence of a period of membrane rupture and was supported by the finding that infection increased as the interval between membrane rupture and delivery increased. Thus, neonatal infection was seen in 16% and chorioamnionitis in 50% of those infants born within 24 h of membrane rupture whereas the corresponding values were 29% and 69% for those infants born >24 h after membrane rupture.

Discussion

Infection as a possible cause of preterm labour has caused much interest recently (Minkoff 1983) and most of the evidence relating to preterm labour is based on two observations. First, all types of infection relating to ascending bacterial invasion, including funisitis, chorioamnionitis, neonatal sepsis and maternal endometritis are more commonly found in preterm births. Second, certain organisms in the vaginal flora are more often found in women with preterm labour or premature rupture of the membranes. Research on vaginal pathogens, however, tends to be limited to the study of only one organism at a time.

In this prospective study we have undertaken a detailed microbiological examination of the genital tract of women presenting in early preterm labour, including anaerobic bacteria, mycoplasmas, ureaplasmas and chlamydiae, and have examined the subsequent development of chorioamnionitis and neonatal infection.

The results of this study show that patients admitted in spontaneous preterm labour between 26 and 34 weeks gestation have significantly more abnormal genital colonization with bacteria, ureaplasmas and mycoplasmas and also have a significantly increased incidence of chorioamnionitis when compared to controls. Neonatal infection was also increased, and *C. trachomatis* was isolated exclusively in the study group.

By strict criteria, almost 50% of patients in preterm labour had abnormal bacterial colonization and 86% were found to carry either ureaplasmas, mycoplasmas or chlamydiae. The classification of what should be considered normal or abnormal vaginal colonization between 26 and 34 weeks is recommended using the strict criteria in Table 3. In three patients vaginal colonization with *C. albicans* was considered normal because no PMNL were found. The two patients from whom *N. gonorrhoeae* was isolated also had PMNL present.

Nearly half the bacteria isolated were anaerobic or microaerophilic which emphasizes the importance of seeking anaerobes in genital swabs from such patients. Wahbeh *et al.* (1984) performed transabdominal amniocentesis on 33 patients in preterm labour and isolated bacteria from seven; anaerobic bacteria were isolated from all seven. Minkoff *et al.* (1984) also found that vaginal carriers of *Bacteroides* sp. were more likely to give birth before 37 weeks.

Study group patients with and without ruptured membranes were considered together because the genital flora on admission to the study was almost identical in the two groups. This together with the finding that subsequent chorioamnionitis and neonatal infection was more common in patients with ruptured membranes would suggest that ruptured membranes are not the result of infection but rather that infection follows rupture. This is supported by Zaaijman *et al.* (1982) who studied spontaneous premature rupture of the membranes in patients who were delivered preterm.

These findings have practical implications for the present approach to the management of preterm labour (Lewis *et al.* 1980). It might be possible to identify those patients at risk of labouring preterm if a high vaginal swab was taken in the second trimester. Minkoff *et al.* (1984) found that carriage of *T. vaginalis* and *Bacteroides* sp. was significantly more likely to result in preterm premature rupture of the membranes and patients who carried ureaplasmas more frequently laboured preterm.

When a woman is admitted in preterm labour an ultrasound scan is recommended to detect congenital abnormality, fetal presentation and estimate birthweight, but perhaps the taking of a high vaginal swab for anaerobic culture should be added to this recommendation.

The results of this study suggest that nearly 50% of women in preterm labour have abnormal vaginal colonization. Careful attention, therefore, should be given to the use of tocolytics if infectious complications of prolonging a pregnancy, where there is intrauterine infection, is to be avoided. Hameed *et al.* (1984) have noted that chorioamnionitis is commonly present where the labour is refractory to tocolytics. The need for high doses of tocolytics to inhibit contractions should therefore alert the attendant to the possibility of intrauterine infection.

Having shown an association between abnormal colonization and preterm labour the question follows: is there a causal relation? It has been suggested that bacterial products may have oxytocic properties though the evidence for this in man is scanty (Kass 1961; Wren 1969). More recently Bejar *et al.* (1981) have shown that many organisms associated with intrauterine sepsis produce phospholipase A_2. This is an enzyme responsible for the release of arachidonic acid from cell membranes. Free arachidonic acid acts as a substrate for prostaglandin production and this may be responsible for the initiation of labour.

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Complement activation, circulating protease inhibitors and pregnancy-associated proteins in severe pre-eclampsia

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Summary. Circulating protease inhibitors, pregnancy-associated proteins and the split product of complement factor 3 (C3d) were measured in 14 women with severe pre-eclampsia and their matched controls. Only the mean levels of antithrombin III were observed to be significantly lower in pre-eclampsia ($P<0{\cdot}02$).

There is general agreement that the immunological status is different in pregnant and non-pregnant women. Nevertheless, there is considerable debate about its biological relevance and its role in the aetiology of specific disorders of late pregnancy, in particular pre-eclampsia (Westergaard *et al.* 1986).

In this study we have examined C3d, a split product of the third complement factor and substances which have been suggested to be secondarily involved in the regulation of the complement cascade such as protease inhibitors and pregnancy-associated proteins in 14 women with severe pre-eclampsia compared with matched controls.

Subjects and methods

Methods

The study included 14 women who developed severe pre-eclampsia at 27 weeks gestation and 14 matched controls, all of them were attending the John Radcliffe Hospital in Oxford during 1982 (Table 1). The matching factors were duration of pregnancy and parity. Pre-eclampsia was defined as a maximum antenatal blood pressure ⩾170 mmHg systolic or ⩾110 mmHg diastolic combined with a rise of at least +30/+20 mmHg from a baseline blood pressure taken in the first half of pregnancy, with *de novo* proteinuria of ⩾0·5 g/24 h which regressed after delivery.

Venous blood samples were taken into EDTA-containing tubes and the plasma separated within 30 min of collection, aliquoted and stored at −70°C. Pregnancy-associated proteins [Schwangerschaftsprotein 1, (SP1); pregnancy-associated plasma protein-A (PAPP-A); pregnancy zone protein (PZP)], protease inhibitors [antithrombin III (AT III); α-$_1$antitrypsin (α-$_1$AT); α-$_2$macroglobulin (α-$_2$M)], and a split product of the third complement factor (C3d) were estimated by electroimmunoassays as described in detail previously (Folkersen *et al.* 1981; Teisner *et al.* 1981, 1982, 1983; Westergaard *et al.* 1984). The differences in levels of the various proteins seen between the pre-eclampsia and control patients were analysed using Student's *t*-test after logarithmic

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Table 1. Clinical characteristics of 14 pre-eclamptic subjects and 14 normal controls matched for gestation and parity.

Gestation at sampling (weeks)		Parity		Infant birthweight (g)		Maximum antenatal blood pressure (mmHg)	
Subjects	Controls	Subjects	Controls	Subjects	Controls	Subjects	Controls
33	31	4 + 0	1 + 1	1400	3565	190/125	110/70
35	36	0 + 0	0 + 0	1720	3445	180/120	135/80
30	29	0 + 0	0 + 0	990	2555	200/120	135/80
36	36	0 + 0	0 + 0	2830	3135	180/115	125/80
30	30	0 + 2	0 + 0	865	2940	200/130	130/70
36	36	0 + 0	0 + 0	1720	3950	160/110	130/80
34	34	0 + 0	0 + 0	1830	3230	165/120	130/70
28	28	0 + 0	0 + 0	1295	3480	200/125	130/80
28	27	2 + 0	2 + 0	1010	3415	200/135	120/75
28	28	0 + 0	0 + 0	820	4000	170/108	130/80
27	28	0 + 1	0 + 1	1310	3260	180/120	120/80
34	34	0 + 0	0 + 0	1575	3640	190/140	120/78
28	28	0 + 1	0 + 0	1020	3125	160/110	130/80
34	34	0 + 0	0 + 0	1900	4200	180/115	125/75

transformation of the data, and the Wilcoxon matched-pairs signed-ranks test.

Results

Figure 1 shows the individual maternal levels of pregnancy-associated proteins, protease inhibitors and C3d in the 14 hypertensive patients and the matched control subjects. Analysis by the Wilcoxon signed-ranks test revealed that the lower levels of AT III and SP1 seen in the pre-eclampsia group were statistically significantly different ($P<0{\cdot}03$). After logarithmic transformation only mean levels of plasma AT III were statistically significantly lower ($P<0{\cdot}02$) in the pre-eclampsia group (Table 2).

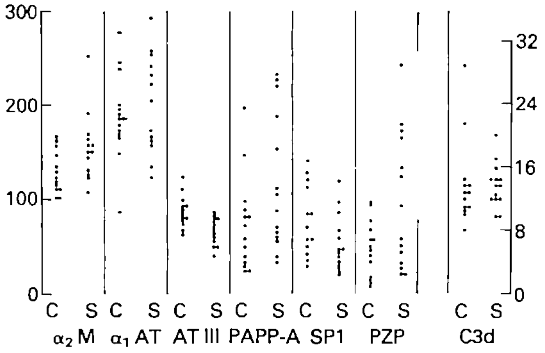

Fig. 1. Scattergram of maternal levels of protease inhibitors, α_2M, α_1AT and AT III (expressed as arbitrary units/l, 100 AU/l being the value in pooled plasma from 50 normal non-pregnant volunteers, left scale); pregnancy-associated proteins, PAPP-A, SP1 and PZP (expressed in i.u./l of WHO reference material for pregnancy associated proteins 78/610, left scale), and C3d (expressed in relation to temperature converted serum designated to contain 1000 AU/l, right scale) in hypertensive subjects (S) and matched controls (C)

Table 2. Maternal levels of protease inhibitors*, pregnancy-associated proteins† and a split product of complement factor 3 (C3d)‡ in women with pre-eclampsia and a matched control group

Factor	Pre-eclampsia group ($n = 14$)	Control group ($n = 14$)	P
Protease inhibitors*			
antithrombin III	1·81 (0·10)	1·90 (0·09)	<0·02
α_1-antitrypsin	2·29 (0·10)	2·26 (0·12)	n s
α_2-macroglobulin	2·19 (0·09)	2·13 (0·09)	n s
Pregnancy-associated proteins†			
SP1	1·65 (0·25)	1·81 (0·23)	n s
PAPP-A	1·97 (0·29)	1·79 (0·36)	n s
PZP	1·82 (0·40)	1·72 (0·36)	n s
C3d‡	1·13 (0·08)	1·11 (0·13)	n s

Results are mean (SD) values following $\log_{10}$ transformation Levels are expressed as follows:

* Arbitrary units/l, 100 AU/l being the value in pooled plasma from 50 normal non-pregnant volunteers

† i.u./l of WHO reference material for pregnancy-associated proteins 78/610.

‡ In relation to temperature converted serum designated to contain 1000 AU/l.

n s , Not significant (Student's *t*-test).

Discussion

Since we have failed to observe differences in complement activation between the two groups of women studied here, we must conclude that either the complement system is not involved in the aetiology of pre-eclampsia, or if it is, that the complement cascade is blocked above the level of C3. The first contention is supported by the lack of evidence for an elevation of circulating immune complexes in this condition (Knox *et al.* 1978; Balasch *et al.* 1981; Mekori *et al.* 1981; Westergaard *et al.* 1986), although other centres have reported contrary findings (Stirrat *et al.* 1978; Houwert de Jong *et al.* 1982; Schena *et al.* 1982; Alanen *et al.* 1984). Our alternative proposition is supported circumstantially by the view that during pregnancy the maternal immunological status is altered (Editorial 1983), with the presence of a blocking antibody strongly indicated. The characterization of these phenomena is far from complete and many pregnancy-associated substances have been put forward as contenders for this role (Cerni *et al.* 1977; Bischof 1981; Stimson *et al.* 1979).

Our data have shown that none of the three pregnancy-associated proteins here is likely either to be involved in the pathogenesis of this condition or to be a useful diagnostic marker. The depressed levels of SP1 seen here in the pre-eclampsia group can be regarded as a consequence of altered placental synthesis seen in association with fetal intrauterine growth retardation which was a feature in the group with pre-eclampsia (Table 1). The discordance between these and other reports is likely to be due to differences in the conditions of sample collection and storage, as well as the design of the clinical studies. The difference observed between mean levels of AT III is in accordance with the findings of studies using plasma (Weenink *et al.* 1983) rather than serum measurements (Gow *et al.* 1983).

It is likely that our findings reflect the alterations in the control mechanisms of the proteolytic load which may occur during pregnancy leading to a re-equilibration of proteases and their inhibitors in cascade systems such as coagulation, fibrinolysis and complement. We are hesitant to recommend AT III measurements as a means of monitoring pre-eclampsia until this phenomenon has been extensively assessed in a prospective study.

Acknowledgments

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Detection of antibodies in pregnancy serum reacting with isolated placental basement membrane collagen

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Summary. Adsorption of human IgG from pregnancy sera to placental basement membrane collagen could be demonstrated by an in-vitro assay. Polystyrene tubes were coated with purified type IV collagen and incubated with serum samples. Bound human IgG was detected using ^{125}I labelled antihuman IgG. Median adsorption levels were 4000 (interquartile range 2500–9500) cpm/ml serum in 25 uncomplicated pregnancies and 21 000 (interquartile range 14 500–44 500) cpm/ml serum in 14 pre-eclamptic women. Specifity of the adsorption reaction could be demonstrated using uncoated tubes and collagenase treated coated tubes, which all showed low binding. In competition experiments with dissolved collagen fractions (type I, III, IV) most effective displacement of binding was observed with type IV collagen. This indicates collagen selectively of the adsorption reaction of human IgG to basement membrane collagen. Our in-vitro studies support immunohistological findings of IgG binding to trophoblastic basement membranes and their ultrastructural abnormalities detected in pre-eclamptic placenta.

Despite the well recognized features of pre-eclampsia: maternal hypertension, proteinuria and oedema, and fetal malnutrition, the underlying aetiology remains unknown. One hypothesis suggests an immunological component in this disease. In general, fetal tissues, particularly the placental villi, represent an antigen stimulus to the maternal organism from early pregnancy. A layer of sialic acid on the villous surface (Rushton 1973), blocking antibodies against fetal antigens and other suppressive effects including hormones are supposed to provide a status of immune tolerance (Scott & Beer 1976, McCornick *et al.* 1971; Faulk *et al.* 1974*a*, *b*). A delicate balance of antigen-antibody concentrations may be responsible for an uncomplicated course of pregnancy. But in pregnancy complicated with pre-eclampsia, an immunological overload (Scott & Beer 1976), elevated levels of circulating immune complexes (Bartl *et al.* 1983; Stirrat *et al.* 1978; Alanen *et al.* 1984) and thickening of trophoblast basement membranes have been reported. Maternal antibodies of the IgG class easily cross the trophoblast cell layer (King 1982) and it was speculated that the structural alterations of the trophoblast basement membrane may be secondary to a deposition of these immunoglobulins (Scott & Beer 1976; Fox 1978; Scott *et al.* 1978). The histological changes together with the clinical symptoms are somewhat similar to those observed in renal diseases associated with immunological reactions against glomerular basement membrane. Thickening of the membrane and deposition of immunoglobulins are typical of various forms of glomerulonephritis, lupus erythematosus, Goodpasture syndrome and in allograft rejec-

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tion were the basement membrane represents a target for the immune system (Kefalides *et al.* 1979; Kefalides 1978; Vracko 1974).

This concept in mind, we designed an in-vitro test to determine whether free circulating antibodies can be found in the serum of pre-eclamptic women, which can react with type IV collagen isolated from human placenta.

Type IV collagen was previously identified as a major structural component of collagenous proteins of basement membranes (Timpl *et al.* 1982).

The aim of the study was: (a) to evaluate an in-vitro assay for detection of human IgG reacting with placental type IV collagen and to test its specifity. (b) To investigate clinically the concentrations of IgG in the maternal serum reacting with the isolated type IV collagen. We actually compared the concentrations found in sera of pre-eclamptic women with those found in uncomplicated pregnancies.

Subjects and methods

Source, selection and collection of human serum

Blood samples were obtained from pregnant women visiting our prenatal clinics or from hospitalized pregnant patients who had been admitted by either our resident in the prenatal clinics or a private physician or transferred from another hospital. All women had a thorough examination for symptoms of pre-eclampsia. Particularly, elevated blood pressure values were double checked by our attending specialist in internal medicine after an interval of 0·5–2 h. Every patient with pregnancy-induced hypertension was assigned with a gestosis index score. This gestosis index was first introduced 15 years ago (Rippmann 1968) and since has been applied for clinical assessment of the severity of disease in our department and by others (Weber 1977; Goecke & Barthel-Wottke 1978). According to the severity of the disease, as determined by the gestosis index (Table 1), we formed group 1 (n=23, GI ≤4) with mild disease and group 2 (n=14, GI >4) with moderate to severe symptoms. Patients with a GI >4 were hospitalized. Twenty-five women with an uncomplicated course of pregnancy served as controls (group 0).

Blood samples from pregnant women were taken by venepuncture during the third trimester. After clotting and centrifugation, serum was stored in aliquots at −20°C and rapidly thawed for use.

For binding studies some of the serum specimens from group 2 had their fibronectin content removed by affinity chromatography on gelatine sepharose (Rhouslahti *et al.* 1982). The 2-ml disposable syringes equipped with a 0·8×50 mm needle and a glassfibre filter were filled with 1 ml gelatine sepharose 4B (Pharmacia, Sweden). Columns were rinsed each with 12 ml PBS (0·15 M NaCl, 10 mM sodium phosphate pH 7·4). Serum samples diluted with PBS (1:2) were applied to the column, followed by elution of unbound material with PBS. Fractions of 0·4 ml were collected and IgG adsorption to type IV collagen was measured.

Isolation procedures

Human placental type IV collagen was isolated as described by Glanville *et al.* (1979) and Sakai *et al.* (1982). Both procedures start with a placental homogenate obtained from fresh placentas immediately after delivery. The tissue was pepsin digested and type IV collagen was obtained by salt precipitation steps at different concentrations and pH. In the Glanville procedure, carboxymethylation, second pepsin digestion and ion-exchange cellulose chro-

Table 1. The gestosis index (GI). The score is calculated by totalling the scores for oedema, proteinuria and blood pressure

	Score			
	0	1	2	3
Oedema	None	Tibial	Generalized	—
Proteinuria protein (g/l)	0·5	0·6–2(+)	2–5(++)	5(+++)
Systolic blood pressure (mmHg)	135	140–155	160–180	180
Diastolic blood pressure (mmHg)	85	90–95	100–105	110

matography (Miller & Rhodes 1982) were added for further purification. The amount of lyophilized type IV collagen from a homogenate of five placentas (2750 g wet weight) from uncomplicated term pregnancies was 0·7 g by the Glanville procedure and twice that amount by the Sakai procedure.

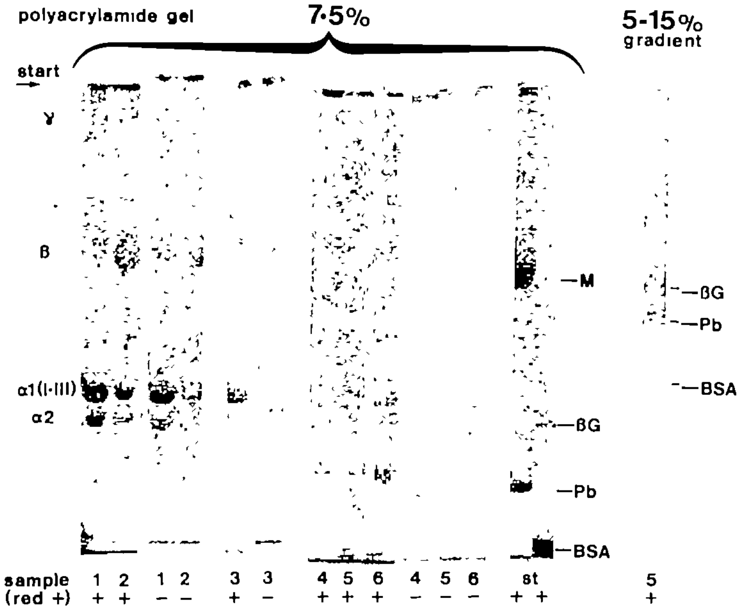
Type I and type III collagen enriched fractions were obtained from the pellet of the 10 mM Na_2HPO_4 precipitation step (Sakai *et al.* 1982), which was dissolved in a neutral salt solvent containing 1 M NaCl, 50 mM Tris/HCl pH 7·5. Type III collagen was precipitated by adding NaCl to 1·8 M. Type I collagen was collected at 2·5 M NaCl (Miller & Rhodes 1982).

For identification and purity control, the collagens were run on SDS-polyacrylamide slab gel electrophoresis (Miller & Rhodes 1982). Samples were compared with commercial preparations under reduced (2-mercaptoethanol) and non-reduced conditions (Fig. 1). Omitting reduction did not alter protein pattern of type I collagen (nos 1, 2). In contrast, the unreduced type III collagen did not penetrate the gel (no. 3). Main bands of reduced type IV collagen appeared at 140, 100 and 70 kd (nos 4, 5, 6). Protein patterns of the collagens were similar to those described in the literature (Miller & Rhodes 1982; Sage *et al.* 1979; Glanville *et al.* 1979; Sakai *et al.* 1982).

Purified collagens were extensively dialysed against 0·2 M acetic acid, lyophilized and finally stored at −20°C. For experiments, they were dissolved in a very small volume of 0·1 M acetic acid, well stirred and the desired buffer was added slowly.

Binding assay

A three step binding assay (coating of polystyrene with type IV collagen, incubation with diluted serum samples, detection of antibodies adsorbed to collagen) was evaluated, optimized and reactions were tested for specifity. To optimize conditions under which collagen adheres to polystyrene tubes (NUNC, Denmark), the fol-


polyacrylamide gel
7·5%
5-15%
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start
γ
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Fig. 1. Electrophoresis of various collagens in SDS-polyacrylamide slab gels (gel thickness: 0·75 mm (7·5%), 1·5 mm (5–15% gradient); protein concentration was 12 μg per lane; reduction by 2-mercaptoethanol). Sample no. 1: type I collagen (placenta); no. 2: type I collagen (calf skin, Calbiochem, USA), no. 3: type III collagen (placenta), no 4. type IV collagen (placenta, Sakai), no. 5: type IV collagen (placenta, Glanville), no 6 type IV collagen (placenta, Sigma, USA), st: myosin (200 kd), β-galactosidase (130 kd), phosphorylase b (98 kd), bovine serum albumin (68 kd).

lowing experimental conditions were examined: (a) amount of substrate (0·5–50μg/ml), (b) pH of coating buffer (pH 4·5–9·5), (c) effect of temperature (6°C and 22°C), (d) different incubation times (2–24 h), (e) washing with PBS or PBS containing 0·05% glutardialdehyde after coating.

Coating efficiency was evaluated either using ^{14}C acetylated type IV collagen (1·5 μCi/mg; Gislow & McBride 1975), or human serum and ^{125}I antihuman IgG, or monoclonal antibodies against type IV collagen and ^{125}I antimouse IgG as detection probe.

For incubation serum samples were diluted with PBS (usually 1:5, other dilutions as indicated) and 500 μl were transferred to the coated tubes. Influence of time (2–24 h) and temperature (6°C, 22°C) were also tested.

In order to determine the class of immunoglobulins binding to the basement membrane collagen, peroxidase labelled antihuman IgG, IgA and IgM (dilution 1:1000, Sigma USA) were used for detection. Since IgG was found to be the only reacting immunoglobulin, in further experiments ^{125}I antihuman IgG (goat, 5·3 μCi/μg, New England Nuclear, USA) was used within 10 days after shipment. A saturation analysis of IgG binding sites with tracer was performed in the range between 10 000 and 120 000 cpm per incubation.

Binding reaction was visualized in the experiments using peroxidase-labelled antibodies by incubation with 0·05% ortho-phenylendiamine, 0·002% H_2O_2 in 0·1 M sodium acetate pH 5 for 20 min at 37°C. The reaction was stopped by addition of H_2SO_4 to a final concentration of 0·5 M.

In experiments with radioactive tracer, tube adsorbed radioactivity was counted in a 'Multiprias' scintillation counter (Packard, USA).

Table 2. Procedure for binding assay

(1) Incubation of polystyrene with 5 μg type IV collagen per 500 μl 20 mM $NaHCO_3$ pH 9·5 for 3 h at 22°C.

●) Washing: 0·05% glutardiadehyde in PBS, PBS, 20% fetal calf serum in PBS.

(2) Incubation with human serum (diluted with PBS to 500 μl) for 2 h.

●) Washing: 20% fetal calf serum in PBS, twice PBS.

(3) Incubation with 100 000 cpm ±5% ^{125}I antihuman IgG per 500 μl PBS for 1 h.

●) Washing: 0·4% Tween 20 in PBS, 6 times.

●) Counting of radioactivity.

Each incubation step was separated from the next by washing procedures. To minimize effects of non specific binding sites, different washing procedures were assessed. Coated tubes were washed with (a) PBS, (b) 0·2% BSA or ovalbumin in PBS, (c) 20% fetal calf serum (Flow Laboratories, UK) in PBS. Influence on excess radioactivity removal by the number of washing steps (2–10) was checked with PBS, 0·2% BSA 0·02% Tween 20 in PBS, 0·4% Tween 20 in PBS.

Specifity of human IgG adsorption reaction was tested in: (a) tubes coated with type IV collagen and uncoated polystyrene tubes, (b) type IV collagen coated tubes incubated with 25 U collagenase type VII (Sigma, USA) dissolved in 1 mM $CaCl_2$, 50 mM Tris/HCl pH 7·4 for 30 min at 37°C followed by PBS washing three times, before serum incubation, (c) co-incubation of serum with dissolved type IV collagen (40 μg/incubation).

Displacement experiments were performed to assess collagen selectivity. In a separate setting various concentrations of type I, III and IV collagens were dissolved in PBS and added to equal volumes of pooled sera from pre-elamptic patients. These samples were then incubated in type IV collagen coated tubes at 6°C for 18 h. The samples were further processed according to the assay procedures. The fibronectin effect on IgG binding behaviour was studied in a similar experiment.

In the main, experiments were performed in tubes coated with the Glanville collagen, but displacement experiments with various collagens and fibronectin were also performed with the Sakai preparation. Incubations were done in triplicate and radioactivity levels were corrected for nonspecific binding effects.

The distribution free rank sum test of Wilcoxon was used for statistical calculations.

Chemicals of analytical grade were purchased either from Merk (GFR) or Sigma (USA). Purified fibronectin was a generous gift from Dr H. Richter (Max Planck Institut für Biochemie, München, GFR).

Results

A three step binding assay (Table 2) demonstrated adsorption of human IgG from

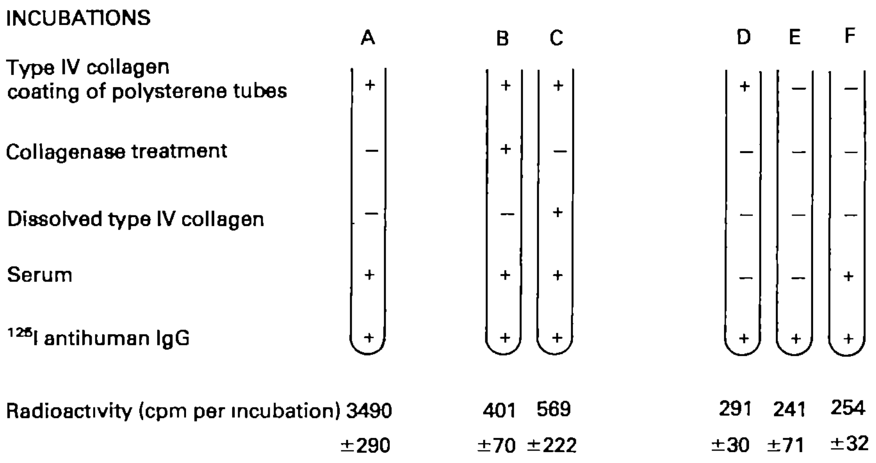

Fig. 2. Specifity of human IgG adsorption to type IV collagen. Pre-eclamptic serum diluted 1:4 with PBS was used. Each radioactivity value represents mean of three determinations ±SD.

pregnancy sera to placental basement membrane collagen.

Optimal coating was observed with 10 µg type IV collagen/ml at pH 9·5 and saturation of the polystyrene surface occurred at between 3 to 6 h at room temperature. In the cold no saturation could be detected even after 18 h. Rinsing the collagen coated polystyrene with diluted glutardialdehyde resulted in a 10% increase of IgG binding values. Maximal IgG adsorption to collagen coated polystyrene was found after 2 h incubation. Levels did not alter, when incubation was prolonged overnight or carried out in the cold.

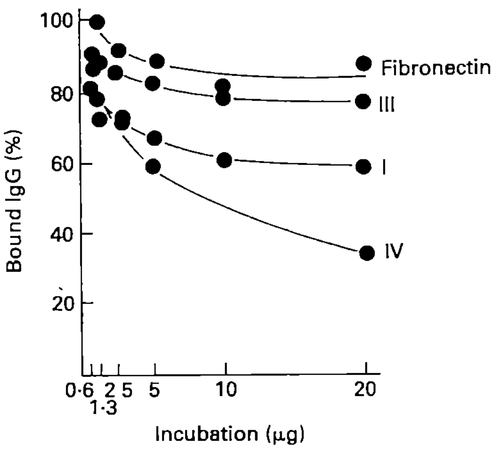

Fig. 3. Experiments on displacement of immobilized type IV collagen bound IgG by dissolved collagens and fibronectin. Note that dissolved type IV collagen is more efficient in displacement than the others.

Class specifity testing of antibodies revealed a selective IgG adsorption to basement membrane collagen. Tracer concentration to obtain saturation of collagen bound human IgG was 100 000 cpm per incubation.

Washing with diluted fetal calf serum reduced the nonspecific binding of ^{125}I labelled antibodies to 0·3–0·8% of total radioactivity. Omitting fetal calf serum increased nonspecific binding three times. Incubations with 0·2% BSA or ovalbumin proved to be less effective than diluted fetal calf serum.

Specifity of IgG adsorption to type IV collagen was demonstrated by different radioactivity values of incubation A compared with others (Fig. 2). Digestion of collagen coat (B) or competition for IgG adsorption by dissolved collagen (C) reduced binding drastically. Nonspecific binding of tracer occurred irrespective of collagen coating (D, E) and adherence of serum IgG polystyrene was also minimal (F).

Collagen selectivity of IgG could be demonstrated by concentration related decrease of IgG adsorption of type IV collagen coated polystyrene, when dissolved collagens of various types were added to the serum incubation (Fig. 3). Interference of fibronectin in the adsorption reaction was negligible (Fig. 3 and Table 3).

Table 3. Experiments on fibronectin interference with IgG adsorption to immobilized type IV collagen. Note that recovery not exceeding 100% suggest an insignificant interference of fibronectin

Serum sample (dil 1:2 with PBS)			Amount of IgG adsorbed to type IV collagen (cpm)	
			A	B
Before fibronectin removal (800 µl applied to the column)			10516±444	8652±528
400 µl fractions eluted from gelatin sepharose				
Fraction number	1 (sample)		1132	912
	2 (sample)		2542	1030
	3		2178	2280
	4		2310	1080
	5	PBS	1014	836
	6		366	828
	7		—	350
After fibronectin removal			Σ9542	Σ7324
recovery			~91%	~85%

In a dilution experiment concentration dependent IgG binding was found only in pre-eclamptic serum (Fig. 4).

Comparing IgG adsorption of pregnancy sera to type IV collagen, pre-eclamptic women had higher levels than those women with an uncomplicated course of pregnancy (Fig. 5). Radioactivity levels measured from samples of group 2 were significantly different from group 1 and group 0, respectively ($P \leq 0{\cdot}001$). Comparing group 1 and group 0, no significant difference could be detected ($P \leq 0{\cdot}1$).

Discussion

Our results suggest a reaction of antibodies of the IgG class present in pregnancy sera with placental basement membrane collagen *in vitro*.

McCornick *et al.* (1971) and Faulk *et al.* (1974*a*, *b*) demonstrated occurrence of IgG bound to trophoblast membranes by immunohistology and elution studies It was speculated, that this IgG might represent blocking antibodies that in some way protect the placenta from maternal cell-mediated immunity. Fox (1978) reviewed histological findings on structural abnormalities in trophoblastic basement membranes in pre-eclamptic placenta and discussed the participation of immune reactions (deposition of antibodies in basement membrane structures) in this phenomenon. However, in-vitro incubation of cryocuts from normal placenta or from EHS sarcoma (a basement membrane producing tumour grown in mice) with sera from pre-eclamptic women showed no reaction of antibodies with basement membrane structures by indirect immunofluorescence (Dr G. Wick, Institut für Allgemeine und Experimentelle Pathologie, Innsbruck, Austria, personal communication). This observation may not contradict our results, since radioimmunoassays are in general more sensitive.

The set up of our assay is similar to 'sandwich' methods, which use immobilized antibody to bind an antigen and radioactive labelled antibody for detection of bound antigen. However, our test has type IV collagen immobilized to select those serum antibodies which interact with the collagen. Radioactive labelled antibodies then react with human IgG adsorbed to type IV collagen (Table 2). Since tracer concentration was in the saturation range, quantitative accessments could be done Measured cpm values are related to a fixed specific activity of the tracer and represent arbitary units. Dilution experiments suggested a linear decline of bound radioactivity only in a logarithmic scale (Fig. 4). Therefore, presented results (Fig. 5) are related to a given dilution (1:5), which seemed to provide adequate antibody concentration at minimal serum consumption.

A significant increase in IgG adsorption to basement membrane collagen was observed in pregnancies complicated by oedema, proteinuria and hypertension. Amount of in-vitro

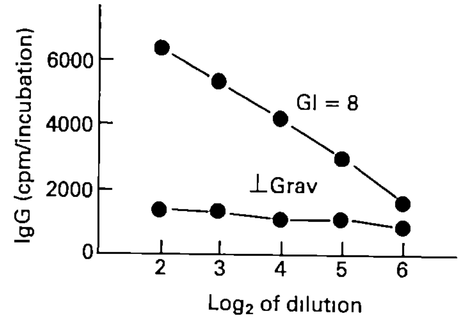

Fig. 4. Effect of serum dilutions with PBS on IgG adsorption reaction. Samples were from an uncomplicated pregnancy and a pre-eclamptic women (GI=8), respectively. Levels were not corrected for non-specific binding.

adsorbed IgG could be related to severity of pre-eclamptic symptoms (Fig. 5). In this context it is intriguing to note, that the circulating IgG concentrations in sera of pre-eclamptic women are lower than in women with an uncomplicated course of pregnancy (Benster & Wood 1970; Studd 1971).

The low concentrations of circulating IgG reported in pre-eclampsia compared to the high amount of collagen adsorbed IgG in our assay rule out a strictly concentration dependent process. This supports specifity of our assay. Likewise, IgG derived from animals (^{125}I anti-human IgG from goat, ^{125}I anti-mouse IgG from rabbit) showed no comparable affinity to collagen. Specifity of the adsorption reaction was also confirmed using uncoated tubes, collagenase treated coated tubes and displacement experiments. All showed low binding (Fig. 2). Type IV collagen selectivity (Fig. 3) was further demonstrated by largest displacement effects in homologous system (type IV collagen: immobilized-dissolved) compared to heterologous systems (type IV collagen: immobilized-type I or III collagen: dissolved).

Recently elevated levels of plasma fibronectin were detected in pre-eclampsia (Tatra *et al.* 1983). This finding is supported by observations of Pulkkinen *et al.* (1984) on torn collagenous structures together with the abundant occurrence of fibronectin within the lobuli of the disrupted tissue of uterine muscle from pregnancies complicated by proteinuria and hypertension. However, from our experiments with fibronectin addition (Fig. 3) or removal (Table 3) we cannot conclude marked influences of fibronectin on in-vitro binding behaviour of IgG to type IV collagen.

Theofilopoulos *et al.* (1981) discussed deposition of immune complexes in various organs with large filtering areas including the placenta. Inflammatory processes may be evoked by deposition of immune complexes along basement membranes due to activation of the complement system. The presence of immune complexes in pregnancy and particularly in pre-eclampsia seem to be still uncertain, since conflicting results have been presented by several investigators. But it might be possible, that immune complexes are involved in the in-vitro adsorption reaction. In preliminary experiments, using a modified assay protocol, increased Clq binding was detected, when IgG adsorption was high.

The hypothesis, that immune reactions are involved in pre-eclampsia found further support in the observation of specific IgG adsorption to basement membrane collagen *in vitro*. This reaction might be concordant with the histologically observed alterations found in placental membranes.

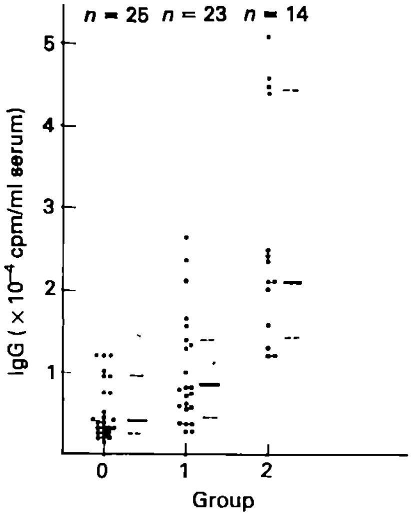

Fig. 5. In-vitro IgG adsorption to type IV collagen measured from sera of normal pregnancies and women with signs of pre-eclampsia. — median (M), - interquartile range (Q_1–Q_3). Group 0 (control). M=4000, Q_1=2500, Q_3=9500 cpm/ml. Group 1 (GI=1–4, mild disease): M=8500, Q_1=4500, Q_3=14 000 cpm/ml Group 2 (GI>4, moderate to severe disease). M=21 000, Q_1=14 500, Q_3=44 500 cpm/ml.

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Immunohistological characterization of endometrial gland epithelium and extravillous fetal trophoblast in third trimester human placental bed tissues

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Summary. The distribution, morphology and antigen expression of endometrial glands, uterine vessels and fetal trophoblast have been studied in third trimester placental bed tissues with a panel of monoclonal antibodies in immunohistochemical techniques. Residual endometrial glands were numerous but often were attenuated or compressed and could only be identified clearly with epithelial cell markers. These glands must be clearly distinguished from vessels and trophoblast in immunological studies of cells in the placental bed. The changing pattern of antigen expression of both maternal glands and fetal trophoblast in placental bed tissues may indicate a form of local regulation of gene expression.

The application of monoclonal antibodies (mAb) to immunohistological techniques has promoted many studies of the diverse villous and extravillous fetal trophoblast populations in uteroplacental tissues (Bulmer *et al.* 1984; Hsi *et al.* 1984; Redman *et al.* 1984; Wells *et al.* 1984*a*; Bulmer & Johnson 1985*a*). However, the predominant maternal epithelial cell population in the pregnant uterus, the columnar epithelium lining endometrial glands, has received less attention. These maternal cells share expression of certain antigens with fetal trophoblast, including epithelial membrane antigens and the trophoblast-leucocyte common antigen system (TLX) recognized by the H316 mAb (Bulmer & Johnson 1985*a*).

Few gland remnants have been identified in the decidua basalis after 20 weeks gestation by light microscopy and a reciprocal relation between the depth of trophoblast invasion and gland destruction has been suggested (Pijnenborg *et al.* 1980). Immunohistological studies have indicated that, in early pregnancy, the epithelial cells of most endometrial glands lose or substantially decrease their expression of class I antigens of the major histocompatibility complex (MHC) (Johnson & Bulmer 1984) and are the focus of an unusual mononuclear cell response (Bulmer & Sunderland 1984; Bulmer & Johnson 1984, 1985*b*). The fate of the glands in later pregnancy is therefore of interest, particularly since their distinction from trophoblast in both morphological and immunohistological studies of placental bed tissues is a potential source of difficulty.

The aim of the present study was to investigate the distribution, morphology and antigen expression of both maternal endometrial glands and extravillous fetal trophoblast within decidua and myometrium in third trimester placental bed

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tissues with monoclonal antibodies reactive with a variety of trophoblast and epithelial markers.

Materials and methods

Tissues

Fifteen normal placental bed biopsies were obtained at elective caesarean section performed for cephalopelvic disproportion, breech presentation, twin pregnancy or a previous uterine scar. Gestational ages ranged from 37 weeks to term. Any abnormal pregnancies including maternal essential hypertension, pre-eclampsia, diabetes mellitus and unexplained intrauterine fetal growth retardation were excluded from the investigation. The tissues were bisected; one half was routinely fixed in 10% formalin and embedded in paraffin wax, and the second half was snap-frozen in liquid nitrogen-cooled isopentane and stored sealed over liquid nitrogen until use. Serial sections (5–7 μm) of frozen tissues were cut in an automated cryostat, air dried at room temperature, fixed in acetone for 10 min at room temperature, air dried overnight, wrapped in foil and stored at −20°C until use

Antibodies

Nine murine monoclonal antibodies and two rabbit polyclonal antibodies were included. Specificities, dilutions, references and sources are detailed in Table 1. The antibodies were selected to provide as clear as possible distinction between trophoblastic elements, endometrial glands and uterine vessels. In term placental tissues H315 and H317 label villous syncytiotrophoblast and some extravillous populations, whereas NDOG1 reacts with villous syncytiotrophoblast alone. In contrast, H316 and markers of low molecular weight cytokeratins react with all villous and extravillous trophoblast populations. HMFG1 and HMFG2 are epithelial membrane markers but are also reactive with a minor population of trophoblast in the amniochorion (Bulmer & Johnson 1985*a*). W6/32 and 61D2 are both directed against monomorphic class I MHC determinants but show different reactivities with trophoblast; W6/32 has been shown to label most extravillous trophoblast within the placental bed, whereas 61D2 reacts with only a minor population of interstitial and endovascular trophoblast (Faulk & McIntyre 1983; Redman *et al.* 1984; Wells *et al.* 1984*a*; Bulmer & Johnson 1985*a*)

Immunohistology

Frozen tissues. Frozen sections were stained using an indirect immunoperoxidase method, as described previously (Bulmer & Sunderland 1984). The primary antibodies used were NDOG1, H315, H317, H316, Monosan anti-keratin, HMFG1, HMFG2, 61D2, anti-Factor VIII related antigen and DAKO-HLA-DR (see Table 1). Peroxidase-conjugated rabbit-anti-mouse Ig and swine-anti-rabbit Ig (Dakopatts A/S, Denmark) were used at a 1:50 dilution in 5% normal human serum (NHS) in Tris-buffered saline (TBS), pH 7·6.

Paraffin-embedded tissues. H315, H317, H316, NDOG1, HMFG1, HMFG2, CAM5.2, anti-ß2-microglobulin and anti-Factor VIII related antigen were used on paraffin-embedded tissues. H315, H317, H316 and NDOG1 were used in a 4-stage peroxidase-anti-peroxidase (PAP) method, as described previously (Bulmer *et al.* 1984). CAM5.2, HMFG1, HMFG2, anti-β2-microglobulin and anti-Factor VIII were used in an indirect immunoperoxidase technique after prior treatment of tissue sections with 1% trypsin (Sigma Chemical Co., Poole, UK) in TBS, pH 7·6, for 20 min at 37°C. Rabbit-anti-mouse Ig, swine-anti-rabbit Ig, rabbit PAP complex, peroxidase-conjugated swine-anti-rabbit Ig and peroxidase-conjugated rabbit-anti-mouse Ig (Dakopatts A/S, Denmark) were diluted 1:30, 1:20, 1:40, 1:50 and 1:50 respectively. Negative controls were performed at all levels and included replacement of primary and secondary antibodies by mouse, rabbit or swine serum as appropriate.

Paraffin-embedded tissues were also stained with haematoxylin and eosin (H&E), Alcian blue at pH 2·5, and the periodic acid Schiff technique (PAS), with and without prior diastase digestion, using standard methods.

Results

Morphology

Varying proportions of decidua and myometrium were identified in all specimens. The spiral arteries showed physiological pregnancy changes (Brosens *et al* 1967) but, although peri-

Table 1. Primary antibodies

Antibody	Specificity	Source/Reference	Dilution
H315	Trophoblast membrane protein	Johnson *et al.* (1981); Johnson (1984), Bulmer & Johnson (1985*a*)	1:1CS (Fr) 1:1CS (Fx)
H316	Trophoblast-leucocyte common antigen	McLaughlin *et al* (1982), Bulmer *et al* (1984), Bulmer & Johnson (1985*a*)	1:1CS (Fr) 1:2CS (Fx)
H317	Placental-type alkaline phosphatase	McLaughlin *et al* (1982, 1984), Johnson & Molloy (1983)	1:1CS (Fr) 1:4CS (Fx)
NDOG1	Syncytiotrophoblast membrane	Sunderland *et al.* (1981), Stirrat *et al* (1983)	1:1CS (Fr) 1:4CS (Fx)
Monosan anti-keratin	Low molecular weight cytokeratin	Sanbio, Netherlands	1:10CS
CAM 5 2	Low molecular weight cytokeratin	Makin *et al* (1984)	1:1CS
HMFG1	Human milk fat globule protein	Burchell *et al* (1983); Unipath, Bedford, UK	1:10CS
HMFG2	Human milk fat globule protein	Burchell *et al.* (1983); Unipath, Bedford, UK	1:1CS
W6/32	Monomorphic class I MHC determinant	Barnstable *et al* (1978), Seralab, Crawley, UK	1:800PE
61D2	Monomorphic class I MHC determinant	Ugolini *et al* (1980), Bethesda Research Laboratories, USA	1:200PE
DAKO-HLA-DR	Monomorphic class II MHC determinant	Dakopatts A/S, Denmark	1:10CS
anti-ß2-microglobulin*	ß2-microglobulin	Dakopatts A/S, Denmark	1:50Ig
anti-Factor VIII*	Factor VIII-related antigen	Dakopatts A/S, Denmark	1:200Ig

* Rabbit polyclonal antibody

CS, Culture supernatant; PE, peritoneal exudate; Ig, purified immunoglobulin; Fr, frozen tissues, Fx, paraffin-embedded tissues

vascular trophoblast was abundant in all tissues, endovascular trophoblast was rarely seen. Interstitial mononuclear and multinucleate trophoblast was a consistent feature in both decidua and myometrium.

Several residual glands were also identified within decidua. Some were lined by columnar epithelium which often showed 'Arias Stella' changes and several were lined by hypersecretory cells with vacuolated ('optically clear') nuclei (Fig. 1a). Interstitial trophoblast was occasionally seen immediately adjacent to gland epithelium. In addition, in all specimens many channels lined by attenuated cells were noted; for these it was not possible to distinguish between residual glands and vascular spaces. The PAS stain did not aid this distinction, since gland epithelium, vascular basement membrane and extravillous trophoblast were all variably PAS-positive. The Alcian blue method did, however, prove helpful; the apical aspect of gland epithelial cells and their secretions, where present, stained blue, whereas vascular endothelium and extravillous trophoblast were always Alcian blue negative (Fig. 1b); but the identity of some channels remained uncertain.

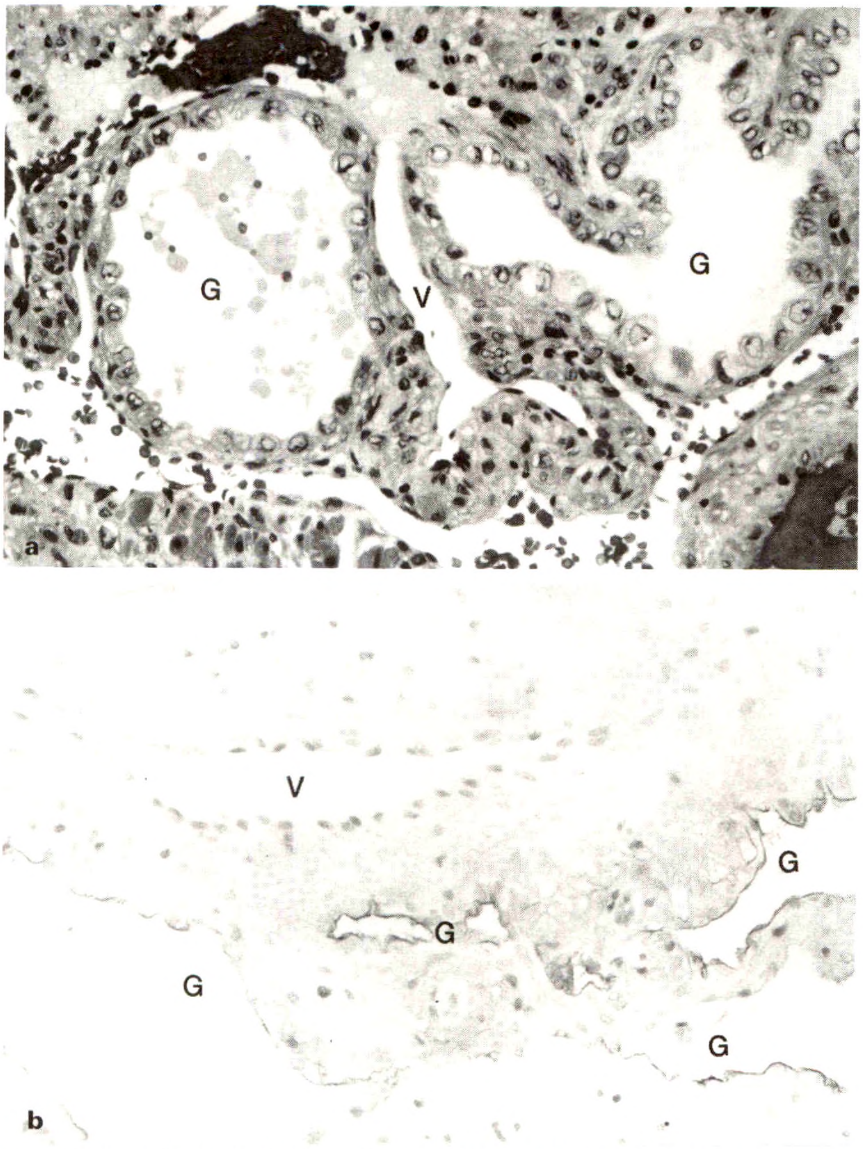

Fig. 1. Sections of formalin-fixed paraffin-embedded term placental bed tissues stained with: (a) haematoxylin and eosin showing vacuolated ('optically clear') nuclei in the epithelial cells lining the endometrial glands × 225. (b) Alcian blue showing staining of the gland epithelium but not of the vascular endothelium × 147. G, Gland; V, vessel.

Immunohistology

Similar results were obtained with both fixed and frozen tissues; these are summarized in Table 2.

Trophoblast membrane markers. Of the trophoblast membrane markers, NDOG1 did not react with any extravillous trophoblast and both H315 and H317 labelled only occasional, randomly distributed, mononuclear and multinucleate trophoblast within decidua and myometrium. In contrast, H316 reacted with all interstitial, perivascular and endovascular trophoblast populations. H316 also labelled the epithelium of all morphologically identifiable glands. In some, reactivity was confined to the basal aspect, whereas others also showed labelling of the apical aspect. H316 did not react with gland secretions. This monoclonal antibody was also reactive with endothelium of many large vascular channels, even in the absence of endo-

Table 2. Reactivity of panel of antibodies with trophoblast, endometrial glands and vessels in term placental bed tissues

Antibody	Extravillous trophoblast	Endometrial glands	Vascular endothelium
H315, H317	±	–	–
H316	+	+	+
NDOG1	–	–	–
Monosan anti-keratin, CAM 5 2	+	+	–
HMFG1	±	+	–
HMFG2*	±	±	–
W6/32, anti-β2-m	+	±	+
61D2	–	±	+
DAKO-HLA-DR	–	–	+
Anti-factor VIII	–	–	+

+, Positive, –, negative; ±, variably positive or negative; * weakly reactive.

vascular or perivascular trophoblast; this labelling of vascular endothelium was confirmed by staining serial sections for Factor VIII-related antigen and was generally confined to larger arterial vessels. H316 also labelled several distorted channels lined by attenuated cells; some of these were identified as vessels by the reactivity for Factor VIII but others were shown to represent residual glands by their reactivity in serial sections stained with HMFG1, Monosan anti-keratin or CAM5.2 (see below).

Cytokeratin markers. CAM 5.2 and Monosan anti-keratin labelled the cytoplasm of all extravillous trophoblast as well as endometrial gland epithelium. There was no reactivity with vessels (Fig. 2.). The reaction patterns observed using H316, Monosan anti-keratin and anti-Factor VIII on serial sections highlighted both the complex distribution of residual distorted glands and vascular channels and the difficulty in distinguishing between them using morphological criteria (Fig. 2)

Epithelial membrane markers. The clearest demonstration of residual gland structures was obtained with HMFG1. The reaction product was situated predominantly on the apical aspect of the epithelium as well as in the gland secretions, highlighting the differing morphological appearances of the glands (Fig. 3). In some, the epithelium showed 'Arias Stella' changes, whereas other glands were lined by hypersecretory cells with vacuolated nuclei. Many glands were lined by attenuated epithelial cells which were intensely reactive with HMFG1, as well as with CAM 5.2, Monosan anti-keratin and H316, but not with anti-Factor VIII. In addition, HMFG1 highlighted numerous long, slit-like channels within decidua (Fig. 3) which also labelled with H316, CAM 5.2 and Monosan anti-keratin. These apparently represented compressed and distorted gland structures which could not be clearly identified, even retrospectively, on sections stained with H & E, Alcian blue or PAS. In contrast to HMFG1, HMFG2 was only weakly reactive with occasional glands within placental bed tissues. However, both HMFG1 and HMFG2 consistently labelled occasional mononuclear and multinucleate interstitial trophoblast cells which were mostly situated deep within the myometrium; there was no relation with the H315 and H317-positive trophoblast which was mostly situated within the decidua.

MHC antigens. W6/32 (reactive with class I MHC products) and anti-β2-microglobulin showed essentially similar reaction patterns, although the former was consistently stronger. These antibodies labelled the vast majority of extravillous trophoblast, including multinucleate cells which were often weakly positive. Maternal decidual cells, myometrium and uterine vessel endothelium were also postive. Reactivity with endometrial gland epithelium was variable. Those glands which retained a columnar lining, even if it was hypersecretory or

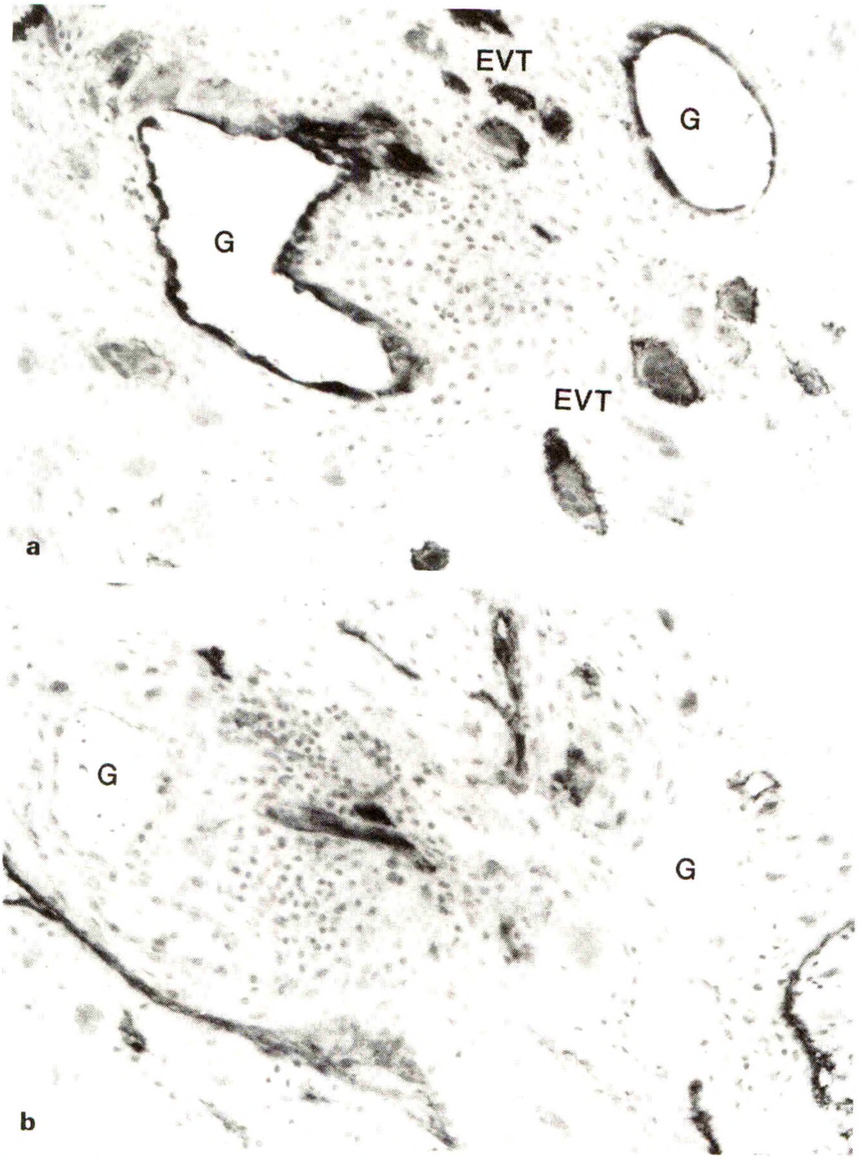

Fig. 2. Serial frozen sections of term placental bed tissues labelled with: (a) Monosan anti-keratin (low molecular weight cytokeratins) showing labelling of extravillous trophoblast and of endometrial gland epithelium. (b) anti-Factor VIII-related antigen showing the complex pattern of small vascular channels and no labelling of gland epithelium or extravillous trophoblast × 147. G, Gland; EVT, extravillous trophoblast.

showed nuclear vacuolation, gave a weak or no reaction with W6/32 (Fig. 4). In contrast, glands lined by attenuated cells or slit-like glands (identified on serial sections stained with HMFG1) were consistently W6/32-positive. The reaction pattern of 61D2, which is also directed against class I MHC products, with maternal decidua, myometrium, vessels and glands was essentially similar to that of W6/32. However, 61D2 did not label the W6/32-positive extravillous trophoblast within decidua and myometrium, as has been reported previously for extravillous cytotrophoblast within the chorion laeve and superficial basal plate at term (Hsi *et al.* 1984; Wells *et al.* 1984*a*). DAKO-HLA-DR labelled many rounded and irregular mononuclear cells within decidua and myometrium, some of which formed aggregates adjacent to endometrial

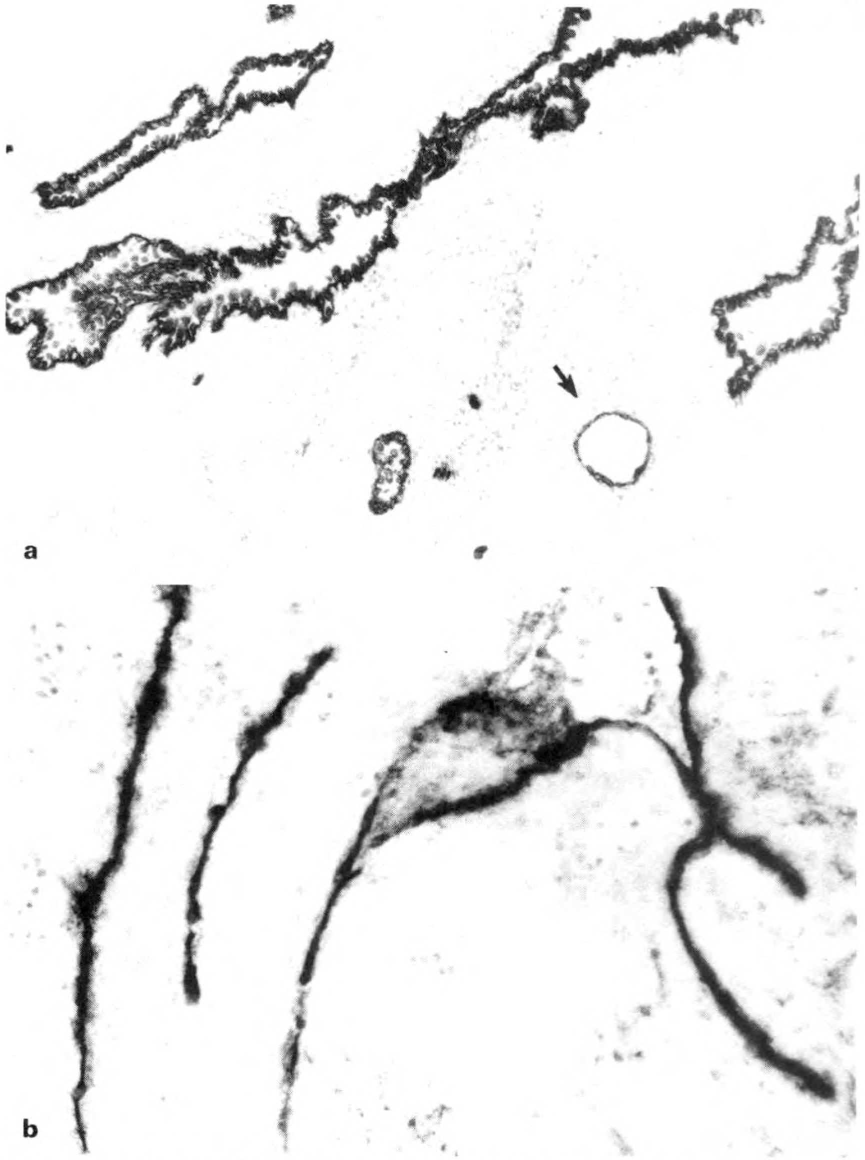

Fig. 3. Frozen sections of term placental bed tissues labelled with HMFG1 (human milk fat globule protein). (a) Most glands are lined by hypersecretory cells but one small gland (arrowed) is lined by attenuated cells × 56. (b) Note the HMFG1-positive compressed slit-like glands lined by attenuated cells × 225.

glands. The endothelium of the majority of uterine vessels was also positive, but DAKO-HLA-DR did not label any extravillous trophoblast in these specimens, nor did it react with any endometrial gland epithelial cells.

Discussion

Numerous glands were demonstrated within the decidualized endometrium in late stages of pregnancy, although many were distorted or compressed and only recognized with specific epithelial cell markers in immunohistochemical techniques. Throughout human pregnancy, the endothelial cells of uterine spiral arteries and arterioles frequently appear swollen or are replaced by endovascular cytotrophoblast (Boyd & Hamilton 1970; Pijnenborg *et al.* 1980). Hence, the distinction between endometrial glands, which sometimes contain blood, and

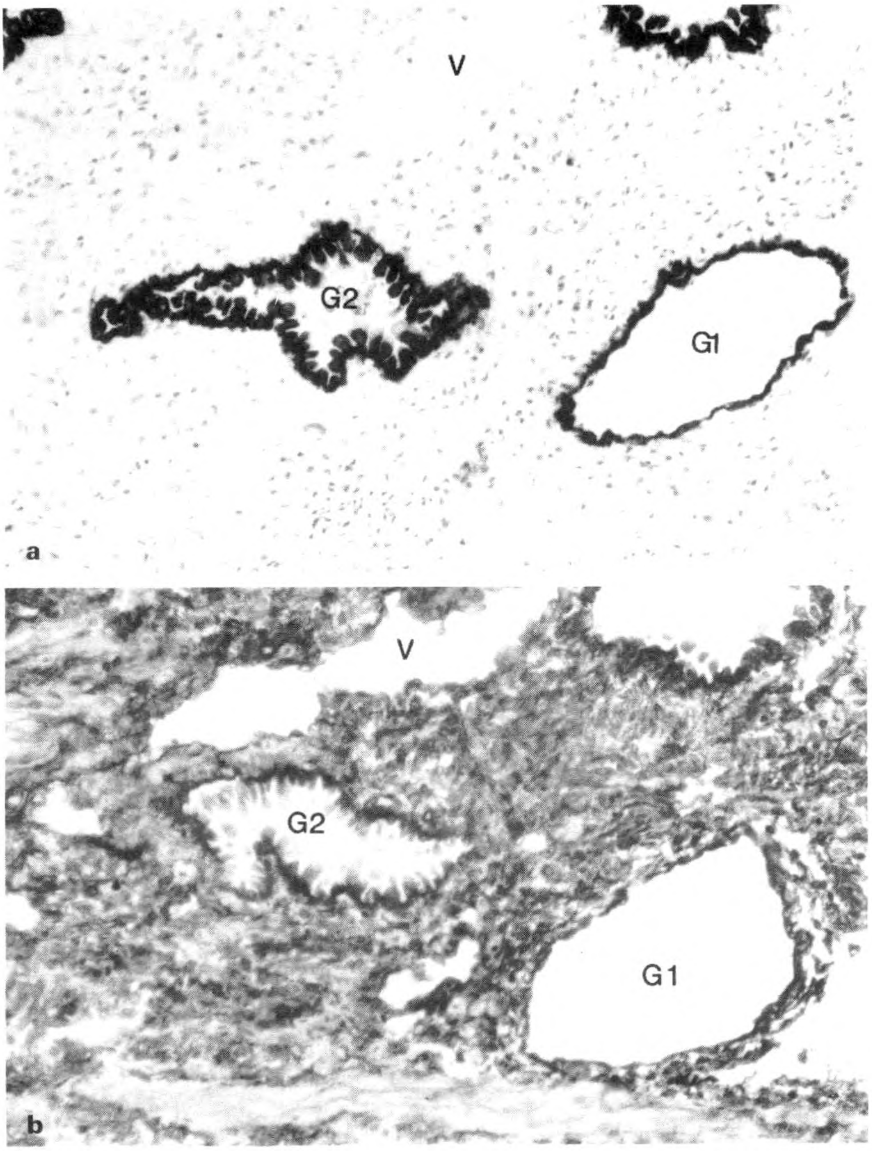

Fig. 4. Serial frozen sections of term placental bed tissues labelled with: (a) HMFG1; (b) W6/32 (monomorphic class I MHC determinants). G1 is lined by attenuated cells and is W6/32-positive, whereas G2 is lined by hypersecretory cells and shows much weaker labelling with W6/32. The vessel endothelium (V) is HMFG1-negative and W6/32-positive × 147.

uterine vessels may be impossible by light microscopy and routine histochemical procedures. This may account for previous reports suggesting that endometrial glands are substantially reduced in number in the second half of pregnancy (Pijnenborg *et al.* 1980).

Monoclonal and polyclonal antibodies have clearly been useful for distinguishing between the diverse populations in human uteroplacental tissues (Sunderland *et al.* 1981; Bulmer *et al.* 1984; Johnson 1984; Bulmer & Johnson 1985*a*), but some limitation of the use of these reagents must be acknowledged. For example, in early pregnancy the epithelial cells of most endometrial glands share certain cell surface antigens with fetal trophoblast (Bulmer *et al.* 1984; Bulmer & Johnson 1985*a*). The antigen expression of both glands and trophoblast also changes with gestation; HMFG1 and HMFG2 react with interstitial trophoblast in the third trimester, but not in early pregnancy. In addition, there are important variations in the expression of MHC antigens by gland epithelial cells. In early pregnancy, the majority of endometrial glands fail to express class I MHC antigens as detected by immunohistology (Johnson & Bulmer 1984). But in late gestation glands lined by attenuated cells express class I MHC antigens normally, in contrast to those retaining their columnar epithelial lining which do not. Conversely, class II MHC antigens have been reported to be expressed by a small proportion of endometrial gland epithelial cells in both non-pregnant tissues and in early pregnancy (Natali *et al.* 1981; Bulmer & Johnson 1985*b*), but were not found to be expressed by either glands or trophoblast in any third trimester tissues. These results suggest that a form of local regulation of gene expression by epithelial cells in these tissues is operative. This regulation may be hormonal or act through cellular contacts. It has been suggested from morphological studies that there may be a reciprocal relation between trophoblast invasion and gland destruction (Pijnenborg *et al.* 1980). Although many glands are clearly not destroyed, it is possible that the invasive potential of genetically disparate fetal trophoblast is influenced by hitherto undetermined products of endometrial glandular epithelium.

Cell surface antigen expression by trophoblast in the superficial zone of the basal plate at term contrasts with that in the deeper decidua and myometrium (Bulmer & Johnson 1985*a*). For example, placental-type alkaline phosphatase is commonly detectable on islands of trophoblast in the superficial basal plate (Johnson & Molloy 1983), but is rarely expressed by cells in the deeper placental bed. This also may indicate local gene regulation and/or differentiation affecting trophoblast at different anatomical sites.

The accurate discrimination between maternal cells and fetal trophoblast in the placental bed has been a source of difficulty for some time. In view of the antigenic sharing with fetal trophoblast, as well as the complex antigenic changes which take place thoughout gestation, endometrial gland epithelial cells are a major potential source of confusion. Markers of cytokeratins and TLX antigens have been used to identify fetally derived cells in decidua (Bulmer *et al.* 1984; Redman *et al.* 1984; Bulmer & Johnson 1985*a*), but the present study has highlighted the difficulty in obtaining a marker reactive with all fetal trophoblast populations throughout gestation which does not also label maternal epithelial cells. Another method which has been applied to the characterization of extravillous cytotrophoblast is an apparent 'doughnut' appearance of the cell nuclei in immunofluorescence after staining with propidium iodide (Faulk & McIntyre 1983; Hsi *et al.* 1984; Wells *et al.* 1984*a*, 1984*b*). It has also been reported that endometrial gland epithelial cells in pregnancy may have vacuolated or 'optically clear' nuclei (Mazur *et al.* 1983). It is worth cautioning, therefore, that these are a potential source of confusion, particularly since morphological features may be less easy to interpret in immunofluorescence.

In conclusion, it has been shown that large numbers of residual endometrial glands, many of which have an attenuated or collapsed appearance, are present in third trimester placental bed tissues. The changing cell surface antigen expression of both the maternal and fetal cell populations in these tissues highlights the difficulty of immunohistochemical studies and suggests that a form of local regulation of gene expression (eg. by steroid hormones) may be operating in uteroplacental tissues throughout gestation and may be important in the control of trophoblast invasion which is a feature of normal human pregnancy.

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Intracellular binding proteins for retinol and retinoic acid in early and term human placentas

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Summary. Specific binding of both [^{3}H]retinol and [^{3}H]retinoic acid was observed in the cytosol fraction from term placentas and specific binding of [^{3}H]retinol but not [^{3}H]retinoic acid was detected in the cytosol fraction from placentas of 8–12 week pregnancies. The elution volume of the bound radioactivity on Sephadex G-100 column chromatography was within the range expected for proteins of molecular weight 14 500, in agreement with the results of others for cellular retinol- and retinoic acid-binding proteins from other tissues. The role of these proteins in mediating the effects of vitamin A on growth and differentiation of the placenta and fetus has yet to be determined.

During gestation both the placenta and the fetus undergo growth and differentiation, processes which in many epithelial tissues are profoundly influenced by vitamin A (Zile & Cullum 1983). Although the adverse effects of vitamin A deficiency on fetal well-being are well recognized, less is known about the role of the vitamin in placental development. In the rat, retinol is essential for normal placental growth and differentiation (Howell *et al.* 1964; Thompson *et al.* 1964; Takahashi *et al.* 1975; Noback & Takahashi 1978) and it has been suggested (Howell *et al.* 1964) that the main role of the vitamin is to maintain the placenta and in this way prevent fetal death which usually occurs in vitamin A deficiency.

Intracellular binding proteins specific for retinol or retinoic acid have been observed in many normal and neoplastic tissues (Chytil & Ong 1978) and it has been postulated that these binding proteins are required for the expression of many of the cellular actions of vitamin A.

In order to gain a better understanding of the role of vitamin A in placental growth and development, we attempted to demonstrate cellular retinol- and retinoic acid-binding proteins in human placentas from early and late pregnancy. Except for a brief mention that such binding proteins could not be detected in the rabbit placenta (Rainier *et al.* 1983), information about cellular retinoid-binding proteins in the placenta of any animal does not appear to be available.

Materials and methods

Normal, term, human placentas were obtained within 30 min of vaginal delivery and placentas at 8–12 weeks gestation were obtained from therapeutic abortions. They were transported to the laboratory on ice and all steps in the preparative procedure were carried out at 4°C. With term placentas, 50 g of villous tissue was excised and washed by shaking for 15 min in 200 ml of isotonic (154 mM) saline and the saline then decanted and discarded. This washing procedure was performed five times. The tissue was then homogenized in a Waring blender with 200 ml of 50 mM Tris-HCl buffer (pH 7·5) containing sodium chloride (200 mM) and phenylmethylsulphonylfluoride (1 mM). The homogenate was centrifuged at 20 000 *g* for 15

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min and the supernatant removed and centrifuged at 105 000 *g* for 1 h. The resultant supernatant (cytosol fraction) was either used immediately or stored for several days at −20°C before use. With the aborted conceptus, placental villous tissue was carefully isolated from the membranes and other fetal tissue by dissection. The villous tissue (2–4 g) was washed twice with 20 ml of phosphate-buffered saline and stored at −20°C. To obtain the cytosol fraction, the tissue was thawed and homogenized in 50 mM Tris-HCl buffer (pH 7·5) containing sodium chloride (200 mM) and sodium azide (0·02%, w/v) using a Potter–Elvehjem-type homogenizer with a motor-driven Teflon pestle. Two millilitres of buffer was used per g of tissue. The homogenate was then made 1 mM in phenylmethylsulphonylfluoride and centrifuged at 105 000 *g* for 1 h.

Cellular retinol- and retinoic acid-binding proteins were detected by a procedure that employs gel filtration chromatography (Saari *et al.* 1980). Samples were prepared for chromatography by incubating 1 ml of the cytosol fraction (10–15 mg of protein) with 20 pmol of tritiated retinol or retinoic acid in the dark at room temperature for 30 min. In experiments aimed at distinguishing between specific and nonspecific binding, the tritiated retinoid was added to the cytosol together with a 200-fold excess of unlabelled retinoid. A 1·6 cm × 100 cm column of Sephadex G-100 was used and was run at 4°C in the dark with 50 mM Tris-HCl buffer (pH 7·5) 200mM in sodium chloride and 0·02% (w/v) in sodium azide, as eluent. The flow rate was 0·3 ml/min and 3 ml fractions were collected.

[^{3}H]Retinol (Amersham International, Amersham, Bucks, UK, specific activity 60 Ci/mmol) and [^{3}H]retinoic acid (Hoffmann-LaRoche, Nutley, New Jersey, USA, specific activity 30 Ci/mmol) were purified before use by high pressure liquid chromatography using conditions modified from those described by Frolik *et al.* (1978). A Partisil 10 ODS 2 column (Pye Unicam) was used with a mobile phase of acetic acid/water/acetonitrile (0·5/20/79·5, by volume) at a flow rate of 2 ml/min. The fractions containing the labelled retinoid were combined, the solvent evaporated under reduced pressure at 30°C and the retinoids dissolved in isopropanol containing 0·1% (w/v) butylated hydroxytoluene. The final concentrations were 3·9 μM for [^{3}H]retinol and 1·8 μM for [^{3}H]retinoic acid. The chemical purity of the unlabelled retinol and retinoic acid used was greater than 95% as assessed by high pressure liquid chromatography.

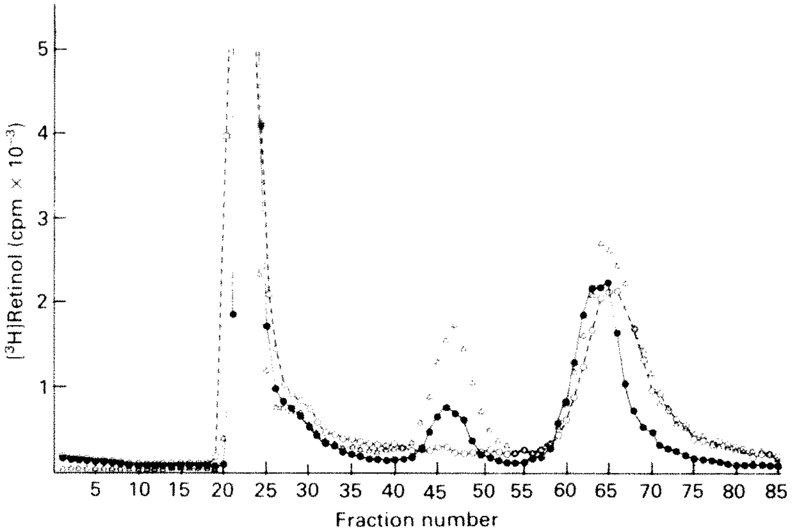

Fig. 1. Sephadex G-100 column chromatography of the cytosol fraction from term placenta after incubation with [^{3}H]retinol in the absence or presence of excess unlabelled retinol or retinoic acid. (See text for procedural details). (△----△) [^{3}H]Retinol only; (○----○) [^{3}H]retinol with 200-fold excess of unlabelled retinol; (●——●) [^{3}H]retinol with 200-fold excess unlabelled retinoic acid.

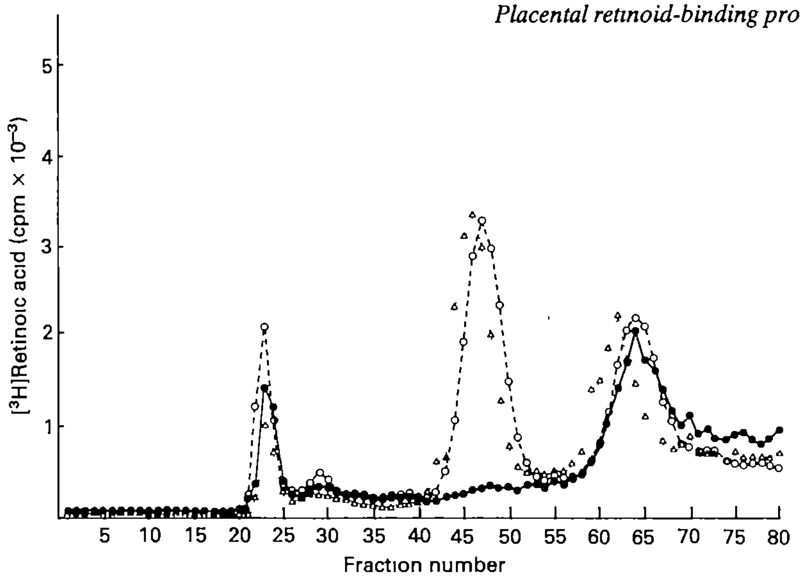

Fig. 2. Sephadex G-100 column chromatography of the cytosol fraction from term placenta after incubation with [^{3}H]retinoic acid in the absence or presence of excess unlabelled retinoic acid or retinol. (See text for procedural details) (△—△) [^{3}H]retinoic acid only; (●——●) [^{3}H]retinoic acid with 200-fold excess unlabelled retinoic acid, (○----○) [^{3}H] retinoic acid with 200-fold excess unlabelled retinol

Protein concentration was assayed by the method of Bradford (1976) with bovine serum albumin as standard. Serum retinol-binding protein concentration was assayed by radial immunodiffusion (Partigen plates, Hoechst). Radioactivity was assayed by liquid scintillation spectrometry using as scintillation fluid toluene/Triton X-100 (2/1, v/v) containing 0·4% (w/v)

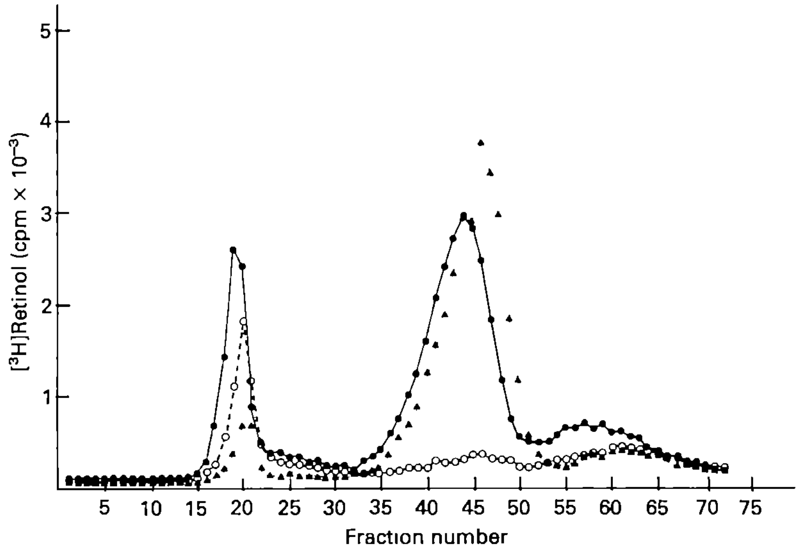

Fig. 3. Sephadex G-100 column chromatography of the cytosol fraction from 8 to 12 week placentas after incubation with [^{3}H]retinol in the absence or presence of excess unlabelled retinol or retinoic acid. (See text for procedural details) (▲---▲) [^{3}H]Retinol only, (○----○) [^{3}H] retinol with 200-fold excess unlabelled retinol; (●——●) [^{3}H] retinol with 200-fold excess unlabelled retinoic acid.

2,5-diphenyloxazole and 0·01% (w/v) 1,4-bis[2-(5-phenyloxazolyl)]-benzene.

Results

The results of investigations of [^{3}H]retinoid binding to cytosol proteins from term placentas are shown in Figs 1 and 2. With either [^{3}H]retinol or [^{3}H]retinoic acid alone, a peak in radioactivity was observed which was eluted midway between the void volume and the included volume of the column (fractions 41–53). This peak was completely suppressed by excess unlabelled retinoid of the same kind, but not by excess unlabelled retinoid of the other type. Radioactivity also appeared at the void volume in both sets of experiments (Figs 1 and 2). This radioactivity was not suppressed by excess unlabelled retinoids and was, therefore, considered to represent nonspecific binding. The radioactivity that appeared at the included volume was considered to consist largely of unbound ligand.

The results obtained in experiments in which the cytosol fraction from early placentas was used are depicted in Figs 3 and 4. When [^{3}H]retinol was used, a relatively large peak of radioactivity was eluted at a position similar to that observed with cytosol from term placentas and this peak was suppressed by excess unlabelled retinol but not by excess unlabelled retinoic acid (Fig. 3). On the other hand, we were unable to demonstrate unequivocally significant specific [^{3}H]retinoic acid binding by cytosol from 8 to 12 week placentas (Fig. 4). Results similar to those shown in Fig. 4 were obtained in several experiments, including one in which the cytosol fraction was irradiated with a long-wave ultraviolet lamp for 16 h at 4°C before incubation with [^{3}H]retinoic acid in an attempt to destroy endogenous retinoic acid (Ong & Chytil 1980).

The Sephadex G-100 column used was calibrated by measuring the elution volume of standard proteins (Fig. 5). The elution volume observed for the specific retinol- and retinoic acid-binding proteins of the placenta (fractions 41–53 of the column) was consistent with a molecular weight of 14 600 reported for these binding proteins in other tissues (Chytil & Ong 1978).

Comment

We have detected specific retinol- and retinoic acid-binding proteins in cytosol fractions obtained by differential centrifugation of homogenates of term human placentas. In the

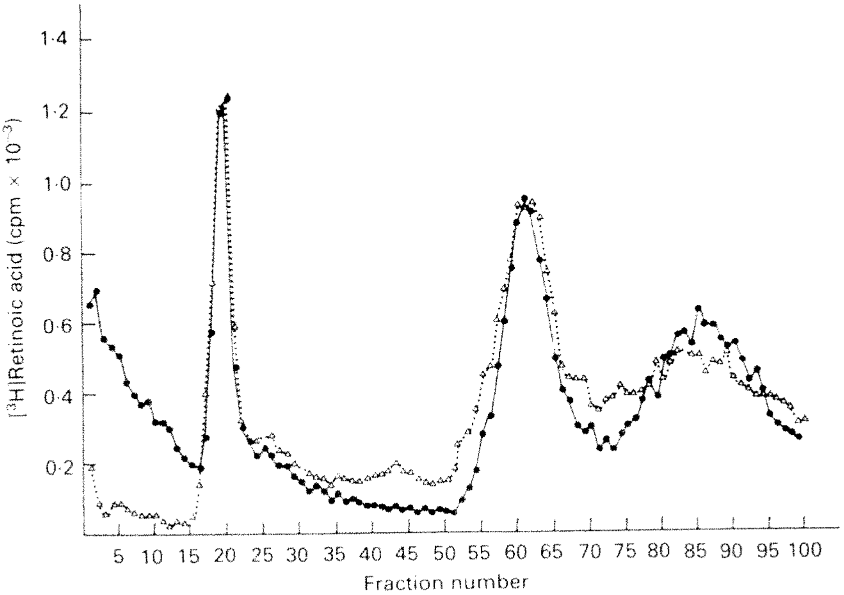

Fig. 4. Sephadex G-100 column chromatography of the cytosol fraction from 8 to 12 week placentas after incubation with [^{3}H]retinoic acid in the absence or presence of excess unlabelled retinoic acid. (See text for procedural details). (△----△) [^{3}H]Retinoic acid only; (●——●) [^{3}H]retinoic acid with 200-fold excess unlabelled retinoic acid.

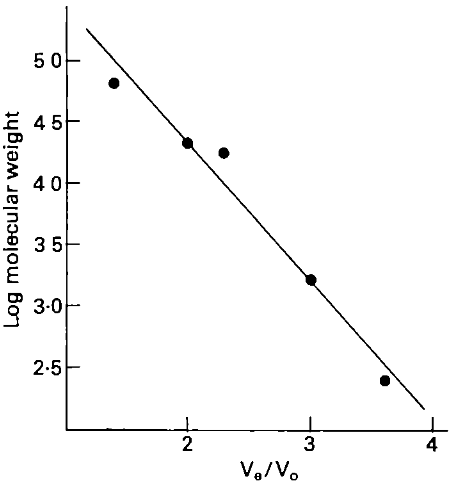

Fig. 5. Calibration of the Sephadex G-100 column using standards of known molecular weight. V_e, elution volume of solute; V_0, void volume of column.

cytosol fraction from 8 to 12 week placentas, specific binding of retinol, but not retinoic acid was observed. Serum contamination of the cytosol fractions is an unlikely explanation for the binding that we observed. The term placental tissue was extensively washed before homogenization and the early placental tissue appeared free of blood. Also, no serum retinol-binding protein could be detected on radial immunodiffusion assay of the cytosol fractions.

Although the results demonstrate specific binding of [^{3}H]retinol to protein in the cytosol of term placentas, there was some decrease in binding in the presence of excess retinoic acid (Fig. 1). It is likely that in our experiments other proteins less specific for retinol were eluted with the cellular retinol-binding protein.

Our inability to demonstrate unequivocally specific binding of [^{3}H]retinoic acid by cytosol fractions from 8 to 12 week placentas may have been due to a lack of sufficient sensitivity of the assay method used. In any case, our results suggest that in the early placenta, specific retinol binding is far more important quantitatively than is specific binding of retinoic acid.

The elution position on Sephadex G-100 chromatography that we observed for the placental retinol- and retinoic acid-binding proteins agrees closely with that reported for these two cellular binding proteins from bovine retina (Saari *et al.* 1980). The two binding proteins have similar molecular weights and are known to be eluted together, although they differ chemically from each other and from the serum retinol-binding protein (Chytil & Ong 1978).

It was early suggested (Bashor *et al.* 1973) that the mechanism of action of vitamin A and steroid hormones at the cellular level was similar, that is, binding of the ligand to protein receptors within the target cells was followed by changes in DNA transcription. It has been difficult, however, to assign definitely and universally a receptor role to the cellular retinol- and retinoic acid-binding proteins since their presence or apparent absence in cells is not always correlated with retinoid-induced effects on proliferation or differentiation (Haussler *et al.* 1984). An alternative suggestion (Adachi *et al.* 1981), that the cytosolic retinoid-binding proteins may function as intracellular transport proteins, may be relevant to the transplacental transfer of retinoids to the fetus. At present, the form of vitamin A that is transferred and the mechanisms involved are unknown.

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Reversibility after female sterilization

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Summary. The factors influencing the result of reversal of tubal sterilization were investigated in a series of 78 patients who requsted this operation during a 5-year period between 1977 and 1982. In the Falope-ring group isthmo-isthmic anastomosis resulted in a 92% pregnancy rate. On the other hand, no pregnancy occurred when the final tubal length after anastomosis was less than 4 cm. Ectopic pregnancy occurred in 5% of the patients.

Although tubal sterilization is a method of permanent contraception, a small but increasing number of women request reversal of sterilization, particularly since the introduction of microsurgical techniques has significantly improved the results (Winston 1977; Gomel, 1977, 1980; Winston & Margara 1980). Studies of the characteristics of patients who require reversal of sterilization have indicated that youth at the time of sterilization and marital instability are the most frequent reasons for requesting reversal of sterilization.

In this study the factors influencing the result of tubal anastomosis are investigated in a series of patients who underwent reversal of sterilization during a 5-year period extending from 1977 to the end of 1982.

Patients and methods

All patients attended the infertility clinic and were selected after careful assessment of their history, their reasons for requesting reversal, their potential for normal pregnancy, gynaecological examination and semen analysis. The reasons for request of reversal were divorce (38 patients), regret (8 patients) and death of child or husband (8 patients). In nine patients the sterilization was primarily suggested or advised by a doctor and in three of them there was serious doubt about informed consent. A hysterosalpingogram was performed if the interval since the last birth was >4 years, if the patient was >30 years of age or after sterilization by electrocoagulation. Laparoscopy was carried out when sterilization had been performed by a surgical procedure or by electrocoagulation. Five patients were excluded as inoperable. A total of 73 patients had surgery during the years 1977–1982. All had had tubal sterilization by either electrocoagulation, Pomeroy ligation or the Falope-ring technique. Ten patients were excluded from the follow-up because they had no sexual relationship.

The clinical characteristics of the 63 patients are summarized in Table 1.

The microsurgical tubal anastomosis was performed with a ×5 to ×20 magnification using a zoom microscope. After incision of the serosa with a 0·1-mm diameter electrosurgery needle the circular muscle coat and mucosa were transected with blunt curved microscissors proximal and distal to the site of sterilization. Under ×20 magnification the quality of the mucosa was inspected. Mucosal fold mobility and the presence of capillary vessels in the mucosal folds together with the presence of a vascular network on the outer layer of the muscle coat were used as criteria for judging the quality of the tissues.

Throughout the operation, 5–6 litres of warm (37°C) Hartmann's solution was showered on the operative field, washing away all blood and enabling bipolar coagulation of all small bleeding points. After resection of the occluded seg-

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Table 1. Clinical data

	Electrocoagulation ($n = 17$)	Pomeroy ($n = 25$)	Falope-ring ($n = 21$)
Age (years)			
≤35	10 (59%)	18 (72%)	18 (86%)
>35	7 (41%)	7 (28%)	3 (14%)
Mean (range)	33 (20–39)	32 (28–42)	31 (26–42)
Parity			
Nullipara	4 (24%)	4 (16%)	3 (14%)
Multipara	13 (76%)	21 (84%)	18 (86%)
Interval sterilization—reversal			
≤5 years	8 (47%)	12 (48%)	17 (81%)
>5 years	9 (53%)	13 (52%)	4 (19%)

ment a 0·4 mm polyethylene splint was introduced into the whole oviduct and uterine cavity using a silver probe as introducer. Before the operation 2 ml of methylene blue diluted in 20 ml Hartmann's solution were injected through a Rubin's cervical canula. If no blue dye was seen after transection of the tube, a transfundal dye injection was made after the cervix was occluded with a modified Shirodkar clamp.

The circular muscle coat, excluding the mucosa, was repaired with six to eight 8/0 nylon sutures starting at the mesentery. When tension on the suture-line was present one 5/0 prolene stitch in the mesentery approximated both tubal segments. In a second layer the overlying serosa was repaired with a running 8/0 nylon. The splint was removed immediately. No further adjuvant therapy such as corticosteroids or hydrotubation was used but 2 g of ampicillin were given daily by mouth for 5 days.

The pregnancy rate was calculated on a 6-month basis using a life table (Querleu 1980). All data were subjected to a χ^2 test analysis.

Results

Table 2 shows the pregnancy rate by age at the time of reversal of sterilization, the time interval between sterilization and reversal operation, the site of anastomosis and the final tubal length, for the three different groups.

There was a high pregnancy rate in two age groups, those aged 25–29 years (94%) and those aged 35–39 (85%). Parity did not affect the pregnancy rate significantly, neither did the interval between the sterilization and the reversal operation. There was a higher pregnancy rate after isthmo-isthmic anastomosis. The differences in pregnancy rates between the different sites of anastomosis was statistically significant in the Falope-ring group. There were no pregnancies where the final tubal length after reversal of sterilization was <4 cm.

The pregnancy rate was significantly reduced (27% *vs* 79% $P<0{\cdot}005$) when the operating time exceeded 150 min. Prolonged operating time occurred in 7 of 25 patients (28%) in the Pomeroy group, in 1 of 17 (6%) in the electrocoagulation group and in 3 of 21 (14%) in the Falope-ring group. The duration of surgery and the pregnancy rate during the 5-year period are tabulated in Fig. 1. From 1980 the pregnancy rate was consistently more than 80% and the mean operating time had gradually decreased from 3 to 1·5 h.

The intrauterine pregnancy rates were 75% for the Falope-ring group, 64% for the Pomeroy group and 70% for the electrocoagulation group. The monthly fecundability (or the mean number of months to conceive) was respectively 0·11 (9 months), 0·05 (20 months) and 0·07 (15 months) for the Falope-ring, Pomeroy and electrocoagulation groups.

Ectopic pregnancy occurred in three patients (5%). The pregnancies were all located at the site of anastomosis which was ampullo-ampullary in one and isthmo-isthmic in two patients. They occurred 2, 3 and 5 months after surgery and there was one case in each of the three groups. Fifteen patients failed to conceive. Obvious reasons for failure included bilateral tubal block (3 patients), hysterectomy (30 months later in one patient) and menopause (1 year later at age of 42 in one patient).

Discussion

The overall pregnancy rate after microsurgical reversal of tubal sterilization of 70% in this study

Table 2. Incidence of pregnancy (number of pregnancies/number of cases) and different factors

	Electrocoagulation	Pomeroy	Falope-ring	Total
Age (years)				
20–24	1/1	0/1	—	1/ 2 (50%)
25–29	1/1	6/6	7/8	14/15 (94%)*
30–34	4/8	6/11	7/10	17/29 (58%)
35–39	6/7	3/4	2/2	11/13 (85%)*
≥40	—	1/3	0/1	1/ 4 (25%)
Interval sterilization—reversal				
≤5 years	6/8	6/12	14/17	26/37 (70%)
>5 years	6/9	10/13	2/4	18/26 (68%)
Site of anastomosis				
isthmo-cornual	4/5	2/4	0/1	6/10 (60%)
isthmo-isthmic	3/3	2/5	12/13**	17/21 (82%)
isthmo-ampullary	3/6	10/14	4/6	17/26 (65%)
ampullo-ampullary	—	2/2	0/1	2/ 3 (67%)
ampullo-cornual	2/3	—	—	2/ 3 (67%)
Total	12/17 (70%)	16/25 (64%)	16/21 (76%)	44/63 (70%)
Tubal length (cm)				
>7	3/5	4/5	13/17	20/27 (74%)
4–7	9/9	12/17	3/4	24/30 (79%)
<4	0/3	0/3	—	0/ 6 (0%)***

$^*P<0{\cdot}01$; $^{**}P<0{\cdot}05$; $^{***}P<0{\cdot}005$.

is similar to rates reported previously (Winston & Margara 1980; Gomel 1980; Seiler 1983). The ectopic pregnancy rate of 5% is also comparable to that of these series. Absence of patency occurred in 4% of the patients and was not a major factor in failure.

The pregnancy rate in this series was affected by the site of anastomosis, confirming the original observation of Winston & Margara (1980). This was evident in the Falope-ring group where a 92% pregnancy rate was obtained after isthmo-isthmic anastomosis. A similar result was previously obtained by Boeckx *et al.* (1977) in an experimental study of reversal of Falope-ring sterilization in rabbits. A lower pregnancy rate was observed for all other sites of anastomosis. An isthmo-isthmic anastomosis was possible in 18%, 20% and 62% of those who had had electrocoagulation, Pomeroy ligation and Falope-ring sterilization, respectively.

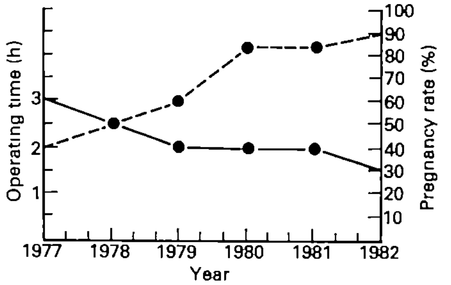

Fig. 1. Pregnancy rate (– – –) and operating time (——) during a 5-year period

The high pregnancy rates of 94% and 84% in the age groups of 25–29 years and 35–39 years were not explained by a high frequency of Falope-ring sterilizations in these groups. Frequency of intercourse may be important; our older women may have been having intercourse more often than average for their age group because of their special desire for pregnancy. In addition, not all patients attempted a pregnancy immediately following reversal of sterilization.

Patients over the age of 40 years were not excluded and this policy was rewarded by one pregnancy in this group. In this study our original observation (Vasquez *et al.* 1980) of a reduced success rate when the interval between sterilization and reversal was prolonged could not be confirmed.

The influence of surgical skill and experience is difficult to investigate. An experimental study by Boeckx *et al.* (1985) has shown the importance of training and experience in microsurgery for restoring the normal tubo-ovarian function after tubal sterilization. In this clinical study the mean operating time decreased gradually from 3 h to 1·5 h and the pregnancy rate during the same period increased from 40 to 90%. These data support the view that surgery for reversal of sterilization should be centralized in order to achieve a consistently high pregnancy rate.

The method of sterilization is important in determining reversibility. This factor can be assessed pre-operatively. Patients who are sterilized by mechanical occlusive techniques such as the Falope-ring can be accepted for reversal of sterilization without laparoscopy unless complications have occurred at the time of sterilization. On the other hand electrocoagulation or surgical procedures can damage the tube to a degree that precludes surgical repair or reduces the tubal length to less than 4 cm. These patients can be treated more effectively by in-vitro fertilization.

Although fecundability following reversal of Falope-ring sterilization is high, care should be taken to apply these rings to the isthmic segment of the Fallopian tube. The ultimate outcome of reversal of tubal sterilization is dependent on the degree of care at the time of sterilization whatever the procedure that is used.

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Evaluation of colposcopy in the postmenopausal woman

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Summary. Cytology, colposcopy and histology findings in 121 postmenopausal and 120 premenopausal women referred to the Oxford colposcopy clinic were compared; 88% of postmenopausal and 69% of premenopausal women were referred by their general practitioners. Cervical smear reports, within the preceding 5 years, were available for 21% of the postmenopausal and 54% of the premenopausal women. Colposcopic assessment was technically unsatisfactory in 53% of the postmenopausal women because the transformation zone was not completely visible, this contributed to a cone biopsy rate of 71% in this group. Only 17% of postmenopausal women with cervical intraepithelial neoplasia (CIN) were managed with local ablative techniques compared with their use in 61% premenopausal patients overall and in over 70% of the women under 35 years. Local ablation was used in 10 of 14 women using hormone replacement therapy. The cytological false negative rate for postmenopausal Papanicolaou class III, IV and V smears was 9% but for persistent class II inflammatory smears it was 43%. Nine of 23 postmenopausal women with persistent inflammatory dyskariosis despite antibiotic or antifungal treatment were found to have colposcopic appearances of CIN and four had microinvasion or invasion. Colposcopy revealed probable microinvasive or invasive disease in 17 postmenopausal women, seven of whom had class II or III cytology.

Until the mid 1970s the standard management for cervical intraepithelial neoplasia (CIN) involved cone biopsy of the cervix, which was both diagnostic and therapeutic. But by 1981 the study group of the Royal College of Obstetricians and Gynaecologists (Jordan *et al.* 1981) had concluded that 'Ideally no patient with cervical intraepithelial neoplasia should be treated unless there has been prior colposcopic assessment.' Following this Singer & Walker (1982) stated that 'at least three quarters of women with cervical intraepithelial neoplasia stage 3 were suitable for treatment using locally destructive procedures.' Whilst this approach has undoubtedly proved successful in dealing with the increasing number of young women presenting with abnormal cervical cytology who wish to maintain their reproductive potential, there is

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scant information about the value of this approach for the postmenopausal patient.

We therefore decided to study the referral cytology, colposcopic appearances, histological diagnosis and subsequent management of all postmenopausal women referred to the Oxford colposcopy clinic with abnormal cervical smears or a clinically suspicious cervix between January 1982 and December 1984. As a comparison we studied all consecutively referred premenopausal women between September and December 1984. Patients were assessed by one of three experienced colposcopists and the cytology double-screened by a consultant cytologist.

In this paper we present and comment on our experience in managing postmenopausal women with abnormal cervical cytology.

Patients and methods

Overall 1080 patients were referred and examined at the Oxford colposcopy clinic between January 1982 and December 1984; 121 of them (11%) were postmenopausal and included six women who had class I cytology but were referred because of a 'clinically suspicious' cervix which on examination revealed benign polyps in each case. All women with abnormal vaginal vault cytology following hysterectomy were excluded from the study. The data for 14 women using hormone replacement therapy are presented separately, leaving a study group of 107 patients.

All 120 premenopausal women referred to the colposcopy clinical between September and December 1984 were studied. Seven had class I cytology but the general practitioner considered the cervix to appear abnormal; healthy ectropia were seen in each case. Five patients with cervical condylomata who were referred from the Sexually Transmitted Disease clinic exhibited cytological and colposcopic wart virus infection (WVI) with no coexistent CIN.

Cytology was performed at the central laboratory in Oxford except in nine postmenopausal and seven premenopausal women who were referred from other District General hospitals within the Region. In these 16 patients cytology was repeated using Ayres spatula and found to correspond with the referral smear in all, except one in which WVI was reported rather than moderate dyskariosis.

Colposcopy was performed using a bivalved Cuscoe speculum and at least one directed cervix punch biopsy was taken in all patients. An attempt was made to display the endocervical canal using a Kogan speculum in all patients where the transformation zone was not completely seen. In particular, coexistent lower genital tract lesions were noted. Bacteriological and virological studies were performed on all patients with 'inflammatory' cytology or a recent history of vaginal discharge.

Our histological criteria for microinvasion included those lesions exhibiting non-confluent tongues of neoplastic cells extending to no further than 3 mm below the basement membrane and without capillary-like space involvement or significant lateral spread.

Statistical significance was tested with the paired t-test and the χ^2 test.

Results

Demographic data

The mean age of the 121 postmenopausal women in the study was 54 years (SD 2·6; range 45–68). The mean duration of the menopause in those not using hormone replacement therapy was 42 months (SD 24·0; range 6 months–18 years). The mean age at referral of the premenopausal women was 31 years (SD 5·5; range 15–51).

The source of referral to the colposcopy clinic of pre- and post-menopausal women differed, although all were resident within the Oxford Region. Of postmenopausal women with abnormal cytology, 88% were referred directly by the general practitioner, compared with 69% of premenopausal women ($P<0·05$), 15% of the premenopausal women were referred by family planning, antenatal or postnatal clinics and 9% by the Oxford Sexually Transmitted Diseases clinic (Table 1).

The referral cytology (Table 2)

Sixty-five (54%) premenopausal patients referred had had a cervical smear taken within the preceding 5 years. In 58 patients this had been reported as class I and in seven patients as class II 'inflammatory—for repeat after treatment' on at least two occasions within the 12 months before referral. Failure of inflammatory dyskariosis to resolve after treatment prompted referral to the colposcopy clinic in these seven patients. Of the 107 postmenopausal patients 22

Table 1. Colposcopy clinic referral patterns of patients with abnormal cytology

Source of referral	Premenopausal patients (%) (n = 108)	Postmenopausal patients (%) (n = 101)
General practitioner	69	88
Family planning clinic	12	0
Sexually transmitted disease clinic	9	0
Ante- or post-natal clinic	3	0
Gynaecology clinic	1	3
Other hospital clinic within region	6	9

Table 2. Details of patients referred with abnormal cytology

					Patients screened within 5 years			
	Premenopausal		Postmenopausal		Premenopausal		Postmenopausal	
Papanicolaou class	n	(%)	n	(%)	n	(% of PAP class)	n	(% of PAP class)
I	12	(10)	6	(6)	6	(50)	2	(33)
II	19*	(16)	23†	(21)	9	(47)	6	(26)
III	64	(53)	46	(43)	38	(59)	10	(22)
IV	18	(15)	26	(24)	8	(44)	3	(11)
V	7	(6)	6	(6)	4	(57)	1	(17)
Total	120	(100)	107	(100)	65	(54·2)	22	(20·2)
Endocervical cells seen in PAP I, II, III	70	(58)	24	(22)				

*Including seven patients with two or more class II inflammatory smears within 12 months of the referral smear
†Including 13 patients with two or more class II inflammatory smears within 12 months of the referral smear

(21%) had had a cervical smear within 5 years of being seen in the colposcopy clinic. In 13 patients (59%) of this sub group, however, class II 'inflammatory' smears had been reported on at least two occasions within the preceding 12 months prompting referral to the colposcopy clinic. In eight patients bacteria or fungi had been positively identified and treated, including *Trichomonas vaginalis* in two, *Gardnerella* in three and *Monilia* in three; cytomegalovirus and herpes simplex virus studies were negative in all 13 patients.

Twenty-five premenopausal and 32 postmenopausal women were referred to the colposcopy clinic with cytology suggestive of invasive cells; all these patients were subsequently found to have either microinvasive or invasive disease. Twelve (48%) premenopausal and 4 (12·5%) postmenopausal women had had 'negative' cervical cytology within 5 years of their referral class IV or V smear.

Endocervical cells were seen in 58% of smears graded class I, II and III in premenopausal women and in 22% of similarly classified postmenopausal smears. Of the 14 women using hormone replacement therapy, endocervical cells were seen in 11 (79%).

Characteristics of the transformation zone

The transformation zone was completely seen at colposcopy in only 50 (47%) postmenopausal women, although in those using hormone replacement therapy it was visible in its entirety in 61%. Thus, 53% of colposcopic examinations in postmenopausal women were unsatisfactory, although in all patients at least a proportion of the transformation zone could be seen with a Kogan endocervical speculum. Although it is a routine technique, in many postmenopausal women examination of the endocervical canal caused pain and troublesome bleeding which limited its use. The distribution of unsatisfactory colposcopic examinations due to incomplete visibility of the transformation zone in premenopausal women was age related (≤25 years 14%; 26–35 years 20%; 36–45 years 39%), this trend was also apparent in oral contraceptive users. The transformation zone was completely visible in 72% of the women who used oral contraceptives, 84% of whom were aged under 35 years.

Other colposcopic appearances

All premenopausal women with class IV and V smears had a colposcopic appearance of at least CIN 3 in those patients where the transformation zone was completely seen, including nine who had features of coexistent WVI. Of the 32 postmenopausal women with class IV and V smears (Table 3), 14 had satisfactory colposcopic examinations but the observations were not consistent; there were eight CIN 3; one CIN plus WVI; two WVI, one microinvasion and two invasive foci in a background of CIN.

Of the 19 premenopausal women with class II smears, seven had persistent 'inflammatory' cytology and their colposcopic findings were CIN 1 in two, CIN 2 in two, CIN 2 plus WVI in one and WVI only in two. All of these patients had negative bacteriological and virological studies. Colposcopic findings in the 13 postmenopausal women with persistent 'inflammatory' class II smears, given that the lesion was not completely visible in a high proportion, suggested CIN 2 in five, CIN 3 in two, microinvasion in two and invasion in two. Eight of these 13 women had proven coexistent monilial, trichomonal or gardnerella cervicitis and five also had severe atrophic vaginocervicitis. The other 10 postmenopausal women with class II 'slightly atypical metaplastic cells, non-inflammatory' cytology all had colposcopic features of CIN, although again the squamocolumnar junction was not visible in a high proportion.

Colposcopic WVI was seen in 12 (11%) postmenopausal women (coexisting with CIN in eight), and in 26 (22%) premenopausal women (coexisting with CIN in 14). Coexistent lower genital tract lesions were seen in 6 (5·1%) premenopausal women (including two with VAIN/WVI and four with multicentric condylomata) and in 12 (11%) postmenopausal women (all exhibiting VAIN or VIN).

Subsequent histological findings (Table 4)

The histological correlation with cytology in our group of premenopausal women was 88% overall but only 66% for class II smears. Histological correlation with referral cytology in our group of postmenopausal women was 83% overall but showed a 43% false negative rate (P<0·01) in smears reported as class II.

In the premenopausal group, four patients with colposcopic CIN 2 had CIN 3 histology, eight with colposcopic WVI had coexistent histological mild dysplasia and one had benign immature squamous metaplasia. In all other premenopausal women premalignant change was no greater than that suspected colposcopically, and in all cases microinvasive and invasive colposcopic suspicion was histologically confirmed. In the premenopausal group 24 (20%) had cone biopsy, 18 because of unsatisfactory colposcopic

Table 3. Postmenopausal patients referred to colposcopy clinic: a comparison of cytology and colposcopic findings

		Cytology (Papanicolaou)				
Colposcopy		I	II	III	IV	V
Normal	6	6 (0)	—	—	—	—
CIN 1	3	—	—	2 (1)	—	—
CIN 2	20	—	1 (4)	6 (7)	0 (2)	—
CIN 3	40	—	0 (2)	10 (15)	8 (5)	—
Microinvasive	8	—	0 (2)	1 (1)	1 (1)	0 (2)
Invasive	9	—	0 (2)	0 (1)	2 (0)	0 (4)
Viral	4	—	1 (1)	—	2 (0)	—
Viral + CIN	8	—	1 (0)	2 (0)	1 (4)	—
Chronic inflammation/ atrophic	9	—	6 (3)	—	—	—
Technically unsatisfactory		—	(14)	(25)	(12)	(6)
	107	6	23	46	26	6

Number in brackets denotes patients in whom colposcopic diagnosis was provisional because technically unsatisfactory.

Table 4. Postmenopausal women referred to colposcopy clinic. a comparison of cytological and definitive histological findings

		Cytology (Papanicolaou)				
Histology		I	II	III	IV	V
Normal (metaplasia or benign polyps)	6	6	—	—	—	—
CIN 1	8	—	3	4	0	—
CIN 2	20	—	2	12	2	—
CIN 3	40	—	2	25	13	—
Microinvasive	8	—	2	2	2	2
Invasive	9	—	2	1	2	4
Viral	1	—	1	0	2	—
Viral + CIN	6	—	2	2	5	—
Chronic inflammation/ atrophic	9	—	9	0	0	—
	107	6	23	46	26	6

assessment and six because of suspected microinvasion which was found histologically to be invasion in two.

Of the 50 postmenopausal women in whom satisfactory colposcopic assessment was possible, punch biopsy histology was of greater severity than expected colposcopically in five (Table 5), two had colposcopic CIN 3 but histological microinvasion and three had colposcopic CIN 2 but histological CIN 3. In eight postmenopausal women, microinvasion suspected colposcopically (although strictly examination was technically unsatisfactory in six) was confirmed histologically and in nine others colposcopically suspected invasive disease was confirmed histologically.

Definitive management

Cone biopsy was performed in 76 (71%) postmenopausal women. In 57 this was because of a technically unsatisfactory colposcopic assessment, including four patients whose cytological grading was significantly worse than the overt colposcopic impression. A further eight postmenopausal women had cone biopsy because of colposcopically suspected microinvasion and 11 because of suspicious invasive cytology despite a normal satisfactory colposcopic assessment. Cone biopsy excision of CIN was incomplete in 12 (16%) postmenopausal women, 10 at the endocervical and two at the ectocervical surgical margins. All postmenopausal patients with incomplete endocervical cone biopsy excision of CIN subsequently had hysterectomy; the two patients with residual ectocervical CIN were managed with laser ablation at a later date. Of the 120 premenopausal patients 24 (20%) had cone biopsy as definitive management and in three of them surgical excision of CIN was incomplete, all at the endocervical margin. Seven out of the eight postmenopausal women with microinvasion had a hysterectomy in the light of the cone biopsy histology. Punch or wedge biopsy was used to confirm those with a colposcopic diagnosis of invasion; subsequent treatment consisted of radical hysterectomy plus radiotherapy or radiotherapy alone.

Local ablation of CIN was used in 18 (17%) postmenopausal women compared with 73 (61%) ($P<0{\cdot}01$) premenopausal patients. This difference was primarily because of the number of technically unsatisfactory colposcopic assessments in postmenopausal women; other factors include the high proportion with cytological or colposcopic suspicions of microinvasive or invasive disease and the lower pain tolerance for outpatient local ablation in other patients. The size of the dysplastic lesion did not appear to influence the decision to perform cone biopsy in our postmenopausal patients. Four postmenopausal women with CIN, suitable for local ablation had vaginal hysterectomy and repair to cure stress incontinence or symptomatic prolapse.

In four of the 14 women using hormone replacement therapy the transformation zone was not entirely seen necessitating cone biopsy to confirm cytological suspicions of CIN. In the other 10 women there was complete correlation

Table 5. Postmenopausal women referred to colposcopy clinic: a comparison of technically satisfactory colposcopic and definitive histological findings

	Technically satisfactory colposcopic assessment (50 patients)										
Histology	Total	Normal	CIN 1	CIN 2	CIN 3	Microinvasive	Invasive	Viral	Viral + CIN	Chronic inflammatory/atrophic	Technically unsatisfactory
Normal (metaplasia or benign polyps)	6	6	—	—	—	—	—	—	—	—	—
CIN 1	5	—	2	—	3	—	—	—	—	—	3
CIN 2	4	—	—	4	—	—	—	—	—	—	16
CIN 3	16	—	—	3	16	—	—	—	—	—	24
Microinvasive	4	—	—	—	2	2	—	—	—	—	4
Invasive	2	—	—	—	—	—	2	—	—	—	7
Viral	1	—	—	—	—	—	—	1	—	—	—
Viral + CIN	4	—	—		—	—	—	—	4	—	2
Chronic inflammation or atrophic	8	—	—	—	—	—	—	2	—	6	1
Total	50	6	2	7	18	2	2	3	4	6	57

between cytology, colposcopy and histology enabling effective local ablation of CIN.

Our experience of outpatient endocervical curettage is limited but we found that a significant number of postmenopausal women have been unable to tolerate the procedure in order that sufficient material, especially stroma, is obtained for reliable histological comment.

Discussion

The colposcope was pioneered in the United States by Stafl *et al.* (1977), and though widely used in Europe it was until fairly recently rejected in Britain because, although a more direct biopsy specimen could be taken, the treatment—cone biopsy—was the same. The situation changed when local ablative treatment began to be used in conjunction with the colposcope (Jordan *et al.* 1979). In Oxford it has long been our impression that such an approach to treatment is best reserved for premenopausal women where our local ablation rate in this study was 61% overall, and over 70% in women under 35 years. In postmenopausal women our local ablation rate was 17% as dictated by the same colposcopic and treatment criteria. Our cone biopsy rate in postmenopausal women, excluding those using hormone replacement therapy, was 71% and we doubt that it could be significantly reduced. British experience and confidence in outpatient endocervical curettage and its difficult histology is limited (Coppleson 1981); certainly only a minority of our postmenopausal patients are able to tolerate the procedure.

While it is well recognized that cytology and colposcopy are complementary to the accuracy of diagnosis of CIN, there are specific problems encountered in the postmenopausal age group. In dry atrophic smears cytoplasm frequently becomes eosinophilic, and nuclear pyknosis and karyorrhexis can assume significant proportions; this appearance together with senile inflammatory changes can lead to substantial difficulty in recognizing cancer cells in atrophic postmenopausal cervical smears (Koss 1979). In addition, poor cellular exfoliation can lead to difficulties detecting mild dyskariosis which is compounded by possible inadequate sampling of the frequently small endocervical transformation zone of the postmenopausal woman. Overall 83% of the postmenopausal women referred had colposcopic evidence, and subsequent histological confirmation, of CIN or invasive disease.

However, while our cytological false negative rate for postmenopausal class III, IV and V smears is acceptable (8·7%), class II inflammatory smears carried an unacceptable 43% false negative rate. This finding causes concern and is largely accounted for by those postmenopausal women with persistent 'inflammatory' smears despite antibiotic or antifungal therapy. With the benefit of knowledge of the subsequent histology, all 'inflammatory' class II smears were reviewed; two postmenopausal smears were reclassified as class III with a viral component. Clearly these women are a hitherto unrecognized 'at risk' group warranting expert cytological and colposcopic assessment.

Only four of the 32 (12·5%) postmenopausal women in our study referred with class IV and V cytology had a cervical smear recorded within 5 years preceding the abnormal smear which prompted colposcopic referral. This compares with 12 of 25 (48%) of the same group of premenopausal women. In recent years much attention has focused on the increase in death rates from cervical cancer in women below 35 (Draper & Cook 1983). While intensive cervical screening for 10 years has reduced the mortality rate by almost 50% in the 35–45 age group (Adelstein *et al.* 1981) in those over 50 years the rate has remained static (Husain 1984). Reports that only 10% of those dying of cervical cancer have ever had a smear perhaps show the futility of a screening programme where the wrong age group has been most intensively surveyed (Spriggs & Bonnington 1976) and in the UK many would disagree with the advice of the Canadian Task Force (1982) to stop screening women over 60 years of age.

Little has been written about the problems of colposcopy in postmenopausal women. Stafl & Mattingley (1973) reported that 12·8% of their colposcopic examinations were 'unsatisfactory'. Chanen & Hollyock (1974) found that 40% of a selected group of patients attending their dysplasia clinic showed an atypical transformation zone extending into the endocervical canal beyond colposcopic observation. In neither of these series was the age of the patients stated. Crompton (1976) found that reversion of the transformation zone into the endocervical canal had occurred in approximately 60% of patients in the over 50 age group, but it is apparent that there is considerable variation in the degree to which this reversion occurs and its effect on the colposcopic assessment of women with abnormal cytology has not been examined. Clinical, cytological and colposcopic 'menopause' do not necessarily coincide; occasionally a menstruating patient has cytological and colposcopic appearances suggestive of a loss of oestrogen effect. Conversely, we have found that 10% of clinically postmenopausal women display cytological and colposcopic patterns reflecting a degree of hormonal activity. The transformation zone was completely seen in only 47% of our postmenopausal group but in 61% of the small group of 14 patients using hormone replacement therapy. It is possible that using topical or systemic oestrogens to aid exposure of the postmenopausal transformation zone could have diagnostic and therapeutic implications.

Colposcopic identification of terminal vasculature in postmenopausal women is difficult and to confuse the picture further, the thin squamous epithelium is subject to trauma and frequently displays petechial haemorrhages or a background of vaginocervicitis which can make identification of specific epithelia less easy (Coppleson *et al.* 1978). We have noticed that a high proportion of atypical epithelia, especially microinvasion, in postmenopausal women take a significantly longer time to demonstrate after the application of 3% acetic acid than in premenopausal women. Preliminary saline and green filter techniques, however, demonstrated atypical, and especially microinvasive, vasculature in all such cases and in our opinion is a most important step not to be discarded

Not specifying age groups, Stafl & Mattingley (1973) found their correlation between colposcopy and biopsy to be 85% accurate; in the remainder the histology was less advanced than expected in 12% and more advanced in 3%. Our correlation with respect to directed punch biopsy in postmenopausal women is 84% accurate in those where the transformation zone was completely seen; in the remainder histology was less advanced than expected in 6% (three patients had colposcopic CIN 3 but histological CIN 2) and more advanced—'false negative'—in 10% (two had colposcopic CIN 3 but histological and three others had colposcopic CIN 2 but histological CIN 3). In no postmenopausal patient did the results of endocervical curettage alter the colposcopist's plan of management. Despite the reassuringly high correlation between colposcopy and subsequent histological diagnosis one can question, given our local ablative rate of 17%, whether colposcopic assessment of the postmenopausal woman is worthwhile, but we regard colposcopy as being most important for the following reasons. Nine out of 23 postmenopausal women referred with persistent inflammatory dyskariosis were found to have CIN and four had colposcopic appearances suggestive of either microinvasion or invasion; colposcopy revealed probable microinvasion or invasive disease in 17 postmenopausal women, seven of whom had class II or III cytology; the low incidence of residual ectocervical CIN following cone biopsy reflects the tailored excision facilitated by preoperative colposcopy.

Given the difficulties with cytological interpretation of the postmenopausal smear our study indicates that there is every need for expert colposcopic assessment of women with repeatedly doubtful or inflammatory cervical smears. The importance of such smears in postmenopausal women should be brought to the attention of general practitioners as well as practising gynaecologists.

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Follicle growth patterns and endocrinological abnormalities in infertile women with minor degrees of endometriosis

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Summary. Eighteen patients whose only demonstrable cause of infertility was a minor degree of endometriosis and whose partners were normal, were investigated prospectively for one menstrual cycle using ultrasonography and endocrine profiles. Twelve cycles appeared to be normal. A luteinized unruptured follicle (LUF) occurred in two cycles and one patient had a follicular cyst. In a further two patients there was inadequate or abnormal folliculogenesis whilst in the last patient the follicle ruptured prematurely. This study describes the variety of endocrinological abnormalities found in women with mild endometriosis, and concludes that, in this series at least, there is a low frequency of LUF.

By combining basal body temperature charts, luteal phase plasma progesterone concentrations and endometrial biopsy, disorders of ovulation (Soules *et al.* 1976; Dmowski *et al.* 1976) and abnormalities of the luteal phase (Grant 1966; Hargrove & Abraham 1980) have been described in infertile patients with endometriosis. More recent studies (Radwanska & Dmowski 1981, Pittaway *et al.* 1983) have failed to confirm any increase in luteal phase defects in these patients when compared with fertile controls.

In infertile patients with endometriosis, Brosens *et al.* (1978) showed a delayed plasma progesterone rise and a delayed fall in follicle stimulating hormone (Koninckx *et al.* 1981) following the gonadotrophin peak. It was suggested that these abnormalities were part of the luteinized unruptured follicle (LUF) syndrome which was said to be present in 79% of patients with minor degrees of endometriosis (Brosens *et al.* 1978). This high frequency has been confirmed using laparoscopy (Lesorgen *et al.* 1984) and ultrasonography (Liukonnen *et al.* 1984). These findings are not supported in comparable studies and there is some criticism of the diagnostic methods (Vanrell *et al.* 1982; Dmowski *et al* 1980). Other investigators have also failed to find an increased frequency of LUF in endometriosis generally (Dhont *et al.* 1984) and in mild disease in particular (Donnez & Thomas 1982).

This study was instigated in order to describe the follicular development and hormonal profiles in infertile patients with minor degrees of endometriosis during one complete menstrual cycle.

Patients and methods

Twenty patients were recruited to the study. In all patients the menstrual cycle was regular and other endocrinological abnormalities such as hyperprolactinaemia and thyroid disorders had been excluded. The partner's semen analysis was normal (Belsey *et al.* 1980). Endometriosis was diagnosed visually at laparoscopy by one

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observer (E.J.T.) and verified by another gynaecologist. Tubal patency was verified by dye instillation. The endometriosis was classified using the revised criteria published by the American Fertility Society (1985). Only patients with minimal or mild endometriosis were included and any patient with adhesions that significantly affected tubal patency or ovarian mobility was excluded.

In the cycle following laparoscopy the patients were scanned daily from about Day 7 until 3 days after follicular rupture or until there was a clear follicular or luteal cyst. Plasma was collected daily for estimation of luteinizing hormone (LH), follicle stimulating hormone (FSH) and oestradiol concentrations over the period when scanning was being performed. Two millilitres of saliva were collected daily by the patient for the assay of the progesterone concentrations from about Day 9 until the next menstruation.

Ultrasonography

This was performed using the full bladder technique (Kratochwil *et al.* 1972) with a Sonoline 3000 sector scanner with 3 MHz output (Siemens, Erlangen). Both ovaries were examined daily and any developing follicles identified. Each follicle was measured in two planes and the measurement was repeated three times. Follicular volume was calculated from the average diameter (E. A. Lenton, E. J. Thomas and R. Harper, in preparation). Rupture was diagnosed by a marked decrease in follicular volume associated with the presence of fluid in the pouch of Douglas. LUF was diagnosed by a maintenance of follicular volume combined with the subsequent loss of follicle wall demarcation and the appearance of intra-follicular echoes (Coulam *et al.* 1982).

Plasma assays

The plasma concentrations of LH and oestradiol were determined by conventional radioimmunoassays. For LH, the reagents (^{125}I-LH and antibody F87) were obtained from the Department of Biochemical Endocrinology, Chelsea Hospital, London and plasma concentrations were expressed as U/l of the First International Reference Preparation of LH (68/40). The LH assay coefficients of variation for the LH assay were 13·4, 9·3 and 7·2% for the high, medium and low quality controls respectively (n = 40).

Oestradiol was measured in a direct radioimmunoassay using commercially available reagents (Steranti ER-155). Coefficients of variation were 8·2 and 10·1% for the high and low controls respectively (n = 30).

Salivary asssays

Progesterone concentrations were determined by a direct radioimmunoassay. The assay is similar to the method reported by Chearskul *et al.* (1982) but uses slightly different reagents (Steranti ER-255) and only 150 µl saliva. Inter-assay coefficients of variation were 15% and 25% for the 600 and 200 pmol/l quality controls respectively (n = 38). Follicular phase progesterone concentrations are normally below the sensitivity of the assay (11 pmol/l) although occasional samples showed concentrations varying between 100 and 200 pmol/l. Salivary progesterone concentrations have been shown to correlate well with plasma progesterone patterns in normal and conception cycles (Zorn *et al.* 1984) and luteal phase levels obtained were approximately 1% of equivalent plasma concentrations.

Data analysis

Each cycle was assessed individually. The date of maximum LH concentrations was assigned as Day 0 (LH −0). Cycles were described as normal if the following criteria were satisfied: (i) follicular rupture occurred within 48 h following Day LH −0; (ii) a mid-cycle gonadotrophin peak; (iii) follicular phase length between 9 and 20 days inclusive (95% confidence limits; Lenton *et al.* 1984*a*); (iv) luteal phase length between 12 and 17 days inclusive (95% confidence limits; Lenton *et al.* 1984*b*); (v) plasma oestradiol levels ≥400 pmol/l on Day LH −1; (vi) salivary progesterone concentrations >300 pmol/l on 3 days out of 5 between LH +3 and LH +7. This requirement was decided following analysis of our own unpublished data of the salivary progesterone levels in conceptions cycles.

Results

Using the American Fertility Society Classification (American Fertility Society 1985) the range of scores of the endometriosis was 1–7 (median = 2). After the endocrine and ultrasound assessment 12 of the 20 study cycles were found to be completely normal. The data from these 12 cycles are shown in Fig. 1.

In two patients data collection was incomplete because scanning was stopped after 10 consecutive days during which no follicle had been found. Saliva collection was continued and normal progesterone concentrations were eventually observed suggesting that the two patients ovulated some time after scanning had stopped. Consequently these data are incomplete and the cycles have been excluded from further analysis. In 6 out of 18 study cycles specific abnormalities of follicular growth were observed. These abnormalities are shown in Table 1 and are described individually below.

Luteinized unruptured follicle

This abnormality was seen in two cycles and in both patients although the cycles were endocrinologically normal, follicular rupture was not observed. In one cycle the follicle persisted after the LH peak but showed no significant increase in size. By Day LH +3 there was loss of follicular wall demarcation and the appearance of intra-follicular echoes (Fig. 2). In the other cycle (Fig. 3) there was a rapid increase in follicular volume following the LH peak and the follicle remained as a clear distinct entity until Day LH +6. Initially it was considered that the rapid increase in volume was more consistent with a follicular cyst rather than a LUF but a recent study has described these particular growth patterns as LUF (Hamilton *et al.* 1985).

Follicular cyst

This occurred in one cycle and showed continuation of cystic growth of the follicle for 4 days after the LH peak. This follicle did not demonstrate loss of follicle wall demarcation or the appearance of intra-follicular echoes and the luteal progesterone secretion was grossly inadequate. LUF has been described as absence of follicular rupture in an endocrinologically normal cycle (Marik & Hulka 1978; Dmowski *et*

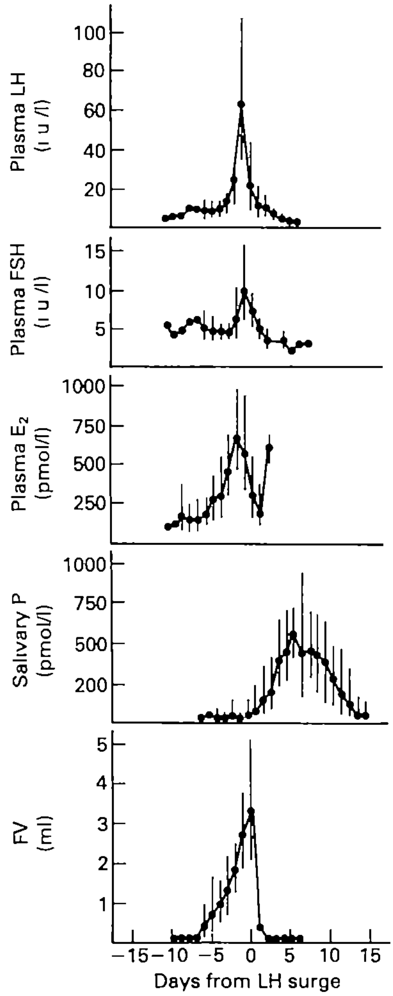

Fig. 1. Geometric mean and 68% confidence limits of luteinizing hormone (LH), follicle stimulating hormone (FSH), oestradiol (E_2) and salivary progesterone (P) concentrations and follicular volume (FV) in the 12 normal cycles.

Table 1. Description of normal and abnormal cycles with regard to absence or presence of the LH surge and follicular rupture and to the normality of the luteal phase

Cycle characteristics –	No. of subjects	LH surge	Follicular rupture	Luteal phase
Normal	12	Present	Yes	Normal
Luteinized unruptured follicle	2	Present	No	Normal
Follicular cyst	1	Present	No	Abnormal
No follicle demonstrated	2	Present	No	Abnormal
Premature follicular rupture	1	Present	Premature	Normal

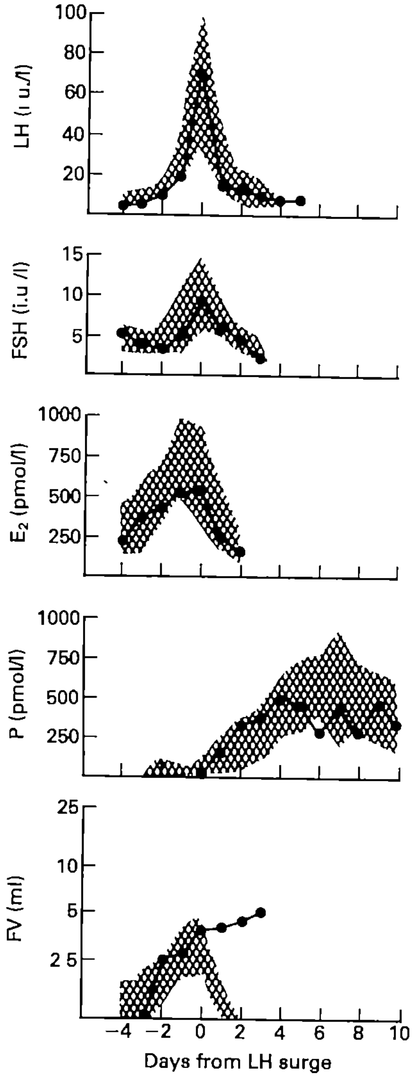

Fig. 2. Individual hormone concentrations and follicle volumes in the first LUF cycle compared with the geometric mean and 68% confidence limits (shaded) of the 12 normal cycles shown in Fig 1

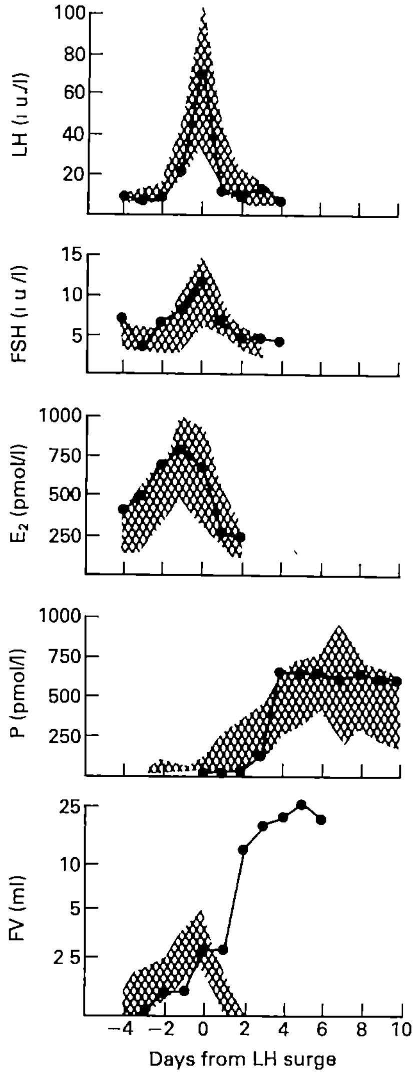

Fig. 3. Individual hormone concentrations and follicle volumes in the second LUF cycle compared with the geometric mean and 68% confidence limits (shaded) of the 12 normal cycles shown in Fig 1.

al. 1980; Brosens *et al.* 1978). This cycle was not endocrinologically normal and therefore was classed as a follicular cyst rather than a LUF. Figure 4 shows the cycle.

Premature follicular rupture

This occurred in one cycle. In a follicular phase of 17 days length rupture was noted between Day LH −1 and Day LH 0. Rupture was verified by the presence of fluid in the pouch of Douglas. The cycle was endocrinologically normal.

No follicle demonstrated

In two cycles no follicle could be demonstrated by ultrasound despite normal gonadotrophin surges and pre-ovulatory levels of oestradiol during the period of scanning. The cycles lasted 17 and 26 days respectively and were characterized by severely inadequate luteal phases. The latter lasted 8 and 15 days respectively and no salivary progesterone level above 300 pmol/l was demonstrated in either. These patients were considered to have gross defects in folliculogenesis leading to clear defects of luteal phase function.

Discussion

This study combines both ultrasonic and synchronous endocrinological data in the assessment of menstrual cycle abnormalities in infertile patients with minor degrees of endometriosis. The combination of rigid selection criteria and detailed investigations has meant that the number of patients who can be studied is inevitably small. However, as great care was taken to ensure that no other diagnosable cause of infertility was present in either partner, except minor degrees of endometriosis, it is reasonable to draw firm conclusions from the frequency of menstrual cycle abnormalities in this group.

To diagnose LUF ultrasonically, observation of the absence of a major change in the follicle is required. The main potential source of error is to fail to appreciate that rupture has occurred and to ascribe the post-ovulatory appearance of the follicle to evidence of in-situ luteinization. This will lead to an excess of false positive diagnoses and this is verified by the absence of false negative diagnoses in the study by Liukonnen *et al.* (1984) when the ultrasound diagnosis was checked laparoscopically. In our study retrospective analysis of the serum gonadotrophin and steroid levels allowed a check on the independently identified time of ovulation. In this way the accuracy of the ultrasound observations are verified and, used in combination with serum endocrinological data, provide a more precise diagnostic method for detecting LUF and other abnormalities of the menstrual cycle.

In three cycles follicular rupture was absent but only two of these cycles conformed to our criteria for LUF. Koninckx & Brosens (1982) proposed that failure of follicular rupture caused low progesterone concentrations in peritoneal fluid in the luteal phase and allowed the implantation of refluxed endometrium and hence endometriosis. In the present series only 3 out of 18 cycles demonstrated failure of follicular rupture giving a frequency in our patients with endometriosis of 17%. The low frequency in a prospectively selected group of patients is at variance with the higher frequencies reported earlier and questions the validity of a causal role for LUF in endometriosis.

No follicle at all was found in 2 of the 18 cycles. There was evidence of ovarian activity since the follicular phase oestradiol levels and gonadotrophin surges were normal. Possible explanations are that the developing follicle was missed during daily ultrasonography or that a number of small follicles were present whose diameters were below the detection threshold of the equipment (7 mm) and that these together were contributing to the oestradiol levels. However, none of the follicles was able to transform into an adequate corpus luteum following the LH surge since the luteal phases were grossly abnormal. Great care had been taken to display the ovarian shadows in every patient and, as there was no anatomical distortion, it is unlikely that a significant follicle would have been missed on several successive days. From the criteria defined by Soules *et al.* (1976) and Dmowski *et al.* (1976) these cycles would have been designated as anovulatory. The frequency of this menstrual cycle abnormality in our patients is 11% comparable to the frequencies of 17% and 10·5% reported in these two studies respectively.

Premature follicular rupture is a phenomenon we have observed in patients with unexplained infertility. This follicle ruptured early in the LH surge. The cycle may have been infertile either because the ovum is too immature for successful fertilization or because it is retained within the deflated follicle. The latter phenomenon has been reported in follicles which have spontaneously ruptured prior to attempts at oocyte recovery for in-vitro fertilization.

Overall, one third of the patients showed defects in follicle growth or rupture which would have been likely to render the cycle infertile. Whilst this demonstrates a relation between endometriosis and defects of folliculogenesis it does not establish a causal link. Recent studies in in-vitro fertilization have shown lower oocyte fertilization rates in patients with endometriosis (Wardle *et al.* 1985; O'Shea *et al.* 1985) and the authors suggested that as yet undefined functional defects in the oocyte may be causal in infertility associated with endometriosis. The fact that all our diagnosed abnormalities were associated with the developing or developed follicle would tend to confirm these findings. What

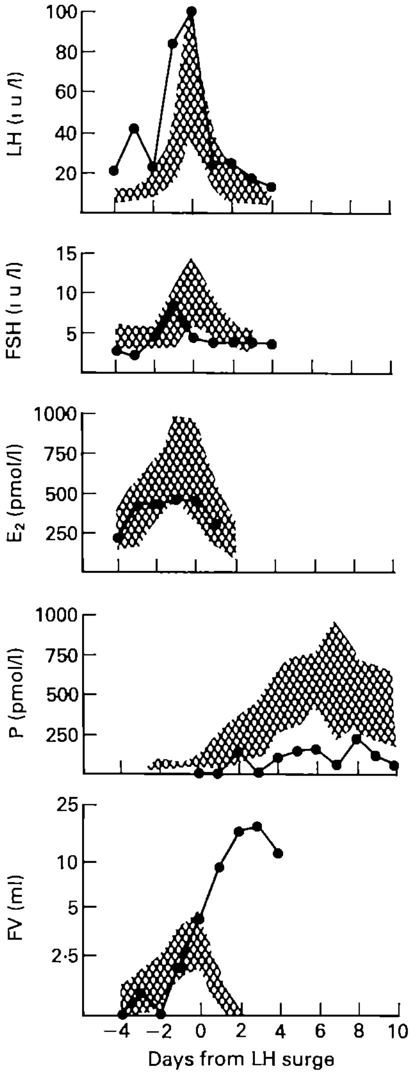

Fig. 4. Individual hormone concentrations and follicle volumes in the follicular cyst cycle compared with the geometric mean and 68% confidence limits (shaded) of the twelve normal cycles shown in Fig. 1.

remains unanswered is whether the endometriosis causes an environment which precipitates poor oocyte function or whether it is the latter and its consequences on folliculogenesis and rupture which is causal in endometriosis.

Twelve cycles were normal and the infertility associated with the finding of endometriosis is therefore unlikely to have been mediated through endocrinological defects. Other mechanisms such as autoimmune phenomena, peritoneal macrophages or prostaglandins could cause the infertility associated with endometriosis in these patients. Overall the mixture of cycle abnormalities in the whole group compares with types of abnormalities diagnosed in patients with unexplained infertility investigated in the same manner in this Department (Lenton 1983) and so an alternative explanation is that these patients have unexplained infertility in which the finding of endometriosis is incidental. Further work is required to resolve this question.

In conclusion we have described defects in follicle growth in endometriosis and have shown a comparatively low frequency of absent follicular rupture in infertile patients with this condition

Acknowledgments

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Endometriosis: its association with retrograde menstruation, dysmenorrhoea and tubal pathology

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Summary. Seventy-five women admitted for sterilization were laparoscoped during menstruation. Retrograde spillage of menstrual blood was observed in 76%. The occurrence of dysmenorrhoea was not associated with spillage of menstrual blood, observed endometriosis or tubal pathology. Mild or stage I endometriosis was detected in 43% of all the women but in only 54% of those who had retrograde spill. Retrograde spill was seen in 97% of those with endometriosis. A significant association ($P<0\cdot001$) was found between endometriosis and tubal damage not due to endometriosis. The implication of these findings are discussed.

Many theories have been advanced both for the presence of endometriosis and for its associated complications (Jackson 1928; Curtis 1932; Sampson 1940; McDonald 1943; Ridley 1968; Ranney 1975; Dmowski *et al.* 1981; Stillman & Miller 1984). The contribution of retrograde menstruation is still uncertain. Furthermore, which particular aspect of endometriosis contributes to dysmenorrhoea or subfertility is still controversial. Tubal distortion, hormonal imbalance, increased peritoneal macrophage phagocytosis or sperm and prostanoid metabolites causing disturbed tubal motility or luteolysis have all been suggested as being responsible for subfertility (Soules *et al.* 1976; Koninckx *et al.* 1980; Sensky & Liu 1980; Muscato *et al.* 1982; Halme *et al.* 1982; Cheesman *et al.* 1983; Drake *et al.* 1983). Retrograde spillage of menstrual blood into the peritoneal cavity with implantation of endometrial fragments may cause endometriosis. It is not clear how often retrograde menstruation occurs and what proportion of these women experience dysmenorrhoea or develop endometriosis.

Patients and methods

The study included 75 patients who were admitted for laparoscopic sterilization during menstruation; they all gave informed consent. The social status of these patients was biased towards the semi-skilled workers. Distribution of parity and age is shown in Table 1.

Before laparoscopy, all the women were asked about menstrual loss, premenstrual symptoms and whether dysmenorrhoea was experienced. Retrograde menstruation observed through the laparoscope ranged from a heavy coating of the pelvic organs with dark menstrual blood to blood staining of the peritoneal fluid in the pouch of Douglas. Contamination by fresh blood as a consequence of laparoscopy was distinguished from retrograde flow by the brighter colour of the former. Menstruation is a particularly useful time to search for active endometriosis because less obvious lesions stand out as dark brown patches or small clusters of bleeding points associated with localized increase in vascularity and local distortion of the peritoneum. In this study, all endometriosis was early/mild stage I disease (American Fertility Society 1985).

Tubal distortion, thickening, peritubular

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Table 1. Parity and specified age groups of patients with and without observed retrograde menstruation

Variable	Retrograde menstruation ($n = 57$)	No retrograde menstruation ($n = 18$)
Age (years)		
26–30	16 (28%)	3 (17%)
31–35	21 (37%)	4 (22%)
36–48	20 (35%)	11 (61%)
Parity		
0	4 (7%)	0 (0%)
1	9 (16%)	5 (28%)
2	29 (51%)	7 (39%)
3	8 (14%)	5 (28%)
≥4	7 (12%)	1 (5%)

Table 2. Distribution of patients with defined gynaecological symptoms and laparoscopic findings among those with and without observed retrograde menstruation

Symptoms and findings	Retrograde menstruation ($n = 57$)	No retrograde menstruation ($n = 18$)
Asymptomatic	15 (26%)	2 (11%)
Dysmenorrhoea	29 (51%)	12 (67%)
Menorrhagia	10 (17%)	5 (28%)
Premenstrual tension	33 (58%)	12 (67%)
Tubal damage	28 (49%)	1 (5%)
Endometriosis	31 (54%)	1 (5%)
Other pathology	4 (7%)	0 (0%)
No pathology	24 (42%)	16 (90%)

adhesions and fimbrial clubbing were considered evidence of tubal damage. The absence of severe endometriotic disease in the study suggested that macroscopic tubal changes were not the direct consequence of endometriosis.

Results

The patients were grouped into those with and without retrograde menstruation and were further subdivided for comparison by parity, age, gynaecological symptoms and laparoscopic findings (Tables 1 and 2). Of the 75 patients 84% were <16 years of age at the menarche. Using χ^2 analysis, it was found that there was no significant difference between those with and those without retrograde menstruation for age or parity.

Retrograde spill was observed in 57 (76%) of the 75 patients. There was no significant difference in the occurrence of menorrhagia, dysmenorrhoea and premenstrual tension between patients with and those without retrograde menstruation (Table 2).

Early endometriosis was detected in 31 (54%) patients with retrograde menstruation, but 97% of those with endometriosis had retrograde menstruation. Tubal damage was found in 26 out of the 31 (84%) patients with endometriosis. Using χ^2 analysis, the association was found to be statistically significant ($P<0{\cdot}001$).

In this study, neither the presence of tubal damage nor endometriosis influenced the prevalence of dysmenorrhoea which was reported by 17 out of 31 (55%) patients with endometriosis and spill, and in 17 out of 28 (61%) patients with tubal damage.

Discussion

The comparatively high prevalence of unexpected endometriosis (43%, 32/75 patients) in this group of women requesting sterilization can be explained in part by the fact that early endometriosis may be detected more readily during menstruation. It is also possible that early endometriosis is more common than is usually suspected. What we cannot determine is whether endometriosis was present before, or occurred after, these women had had their children. What is obvious, however, is that mild endometriosis is common in parous women. The probable beneficial effects of pregnancy may thus be limited to existing disease. Women remain at risk of endometriosis as long as menstruation is occurring.

The frequency of retrograde spill of menstrual blood into the pelvic cavity was found to be even higher (76%) than the 50% reported by Goodall (1944) who performed laparotomy during menstruation.

There was no indication that spillage was confined to any particular age group or affected by parity (Table 1). Retrograde spill may be a common occurrence in all menstruating women but may not occur with every cycle Although retrograde menstruation and implantation of shed endometrial cells remains a recognized and plausible hypothesis for the aetiology of endometriosis (Sampson 1940; Ridley 1968), only half our patients were shown to have developed the condition. Furthermore, neither the presence of early endometriosis nor spillage of menstrual blood into the peritoneal cavity contributed to the occurrence of dysmenorrhoea

Meyer (1919) first proposed pelvic infection as an important pre-requisite for the implantation of endometrial cells and the development of endometriosis This contention finds support in our current study which demonstrated a significant association between tubal damage and the presence of endometriosis.

Subfertility associated with the detection of mild endometriosis is a puzzling situation confronting both patients and practitioners alike Our results suggest that in these patients, tubal damage as a consequence of past, chronic or subclinical infection may play an important role The presence of infection and pelvic pathology (Sampson 1927) can also account for the increased peritoneal fluid, containing macrophages and prostanoid derivatives, that is currently advanced as causes of subfertility associated with endometriosis (Halme *et al* 1982, Drake *et al.* 1983).

No doubt, endometriosis *per se* can give rise to an inflammatory response, an explanation favoured by Drake *et al* (1983) The close association between retrograde spill, tubal damage and endometriosis demonstrated in this study encourages further consideration of Meyer's original contention (Meyer 1919).

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Follicular fluid α_1-antitrypsin—correlation with fertilizing capacity of oocytes

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Summary. Follicular fluid and serum concentrations of α-antitrypsin (α_1-AT) were determined by radial immunodiffusion in 72 samples obtained from 33 infertile women undergoing in-vitro fertilization and embryo transfer. A statistically significantly lower concentration of α_1-AT was found in follicular fluids from which mature oocytes were recovered (mean 1·52, SE 0·06 g/l) than in those yielding immature oocytes (mean 2·96, SE 0·22 g/l). There was also a significantly higher rate of fertilization (85%) for oocytes from follicular fluids with α_1-AT concentrations of $\leq$2·0 g/l than for those obtained when the α_1-AT concentration was >2·0 g/l (only 25%). The mean follicular fluid α_1-AT concentration (1·52, SE 0·06 g/l) of follicles yielding mature oocytes was significantly lower than the relevant mean serum concentration (3·17, SE 0·10 g/l). There was, however, no significant difference between follicular and serum concentration of α_1-AT in the group yielding immature oocytes or in the serum concentrations between the different oocyte maturity groups. The measurement of follicular α_1-AT may be a useful adjunct in predicting which oocytes are mature and likely to be fertilized.

Evidence in the literature suggests that certain biochemical changes occur in the genital tract secretions and tissues at different times of the menstrual cycle and early gestation. These include the accumulation of proteins and in particular proteases and antiproteases (Schumacher & Pearl 1968; Schumacher *et al.* 1977; Dabich & Sommerville-Owens 1978; Tauber 1979). The significance of these changes remains unclear. It is probable that a fine balance between protease and antiprotease activity in the genital tract fluid and tissue respectively at different times of the cycle ensures the optimum environment for sperm capacitation, oocyte fertilization and successful implantation of the embryo (Dabich & Andary 1974; Denker 1977).

Alpha$_1$-antitrypsin (α_1-AT) is the major antiprotease in human serum, accounting for up to 90% of serum antiprotease activity (Jacobson 1955). Schumacher & Pearl (1968) and Schumacher *et al.* (1977) reported that cervical mucus α_1-AT concentration was lowest at midcycle when serum oestrogens are at peak levels. Bagdasarian *et al.* (1981) demonstrated that ovarian stromal cells contain α_1-protease inhibitor, the major serum protease inhibitor, and they suggested the possibility of synthesis of this antiprotease by these cells. Although they were unable to explain the possible function of this antiprotease at the ovarian level, they suggested that it might have a part to play in the 'proteolytic' event of ovulation.

To date there are no published data relating the presence and concentrations of α_1-AT in follicular fluid to the quantity, maturity and ability to be fertilized of oocytes recovered.

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We therefore set out to analyse retrospectively the concentration of α_1-AT in follicular fluid and serum obtained from patients undergoing in-vitro fertilization and to compare the values obtained with the morphological classification of the oocyte maturity and insemination outcome with regard to subsequent fertilization and cleavage.

Patients and methods

Thirty-three couples undergoing in-vitro fertilization and embryo transfer for prolonged infertility were studied. The cause of infertility included tubal pathology (25), unexplained infertility (7) and male infertility (2). Tubal pathology and male infertility coexisted in one of these couples. The mean age of the women was 33·1 (SD 3·4 range 27–39) years. All except one of the men had produced satisfactory semen samples: sperm density >25 × 10^6/ml; >50% progressive motility and less than 30% abnormal forms, one man had oligospermia and a high percentage of abnormal forms (sperm density <3·0 × 10^6/ml, 70% abnormal).

Ovarian stimulation and follicular monitoring

Ovarian stimulation for multiple follicular growth was induced with either clomiphene citrate (Clomid; Merrell-Dow Pharmaceuticals Ltd., UK) or human menopausal gonadotrophin (Pergonal; Serono Laboratories Ltd., UK) alone or a combination of the two. The regimen utilized in any individual was based on previous knowledge of that patient's responsiveness. Follicular growth was monitored with ultrasound alone. An ovulatory dose of human chorionic gonadotrophin (Profasi; Serono Laboratories Ltd., UK) was administered intramuscularly when the average follicular diameter was >17mm. Oocyte recovery was carried out by laparoscopy 32–34 h later using a double lumen aspiration needle (Kovacs *et al.* 1984).

Immediately before oocyte recovery 10 ml of venous blood was obtained from the antecubital vein and allowed to clot. The serum was separated and stored at −20°C. All follicular fluid samples were spun to rid them of cellular material when the oocyte had been recovered and stored at −20°C. Blood stained samples were excluded from the analysis.

Oocyte maturity was assessed immediately after recovery and scored as mature, borderline mature or immature based on the quantity, degree of dispersal and mucification of the cumulus mass and the general appearance of the oocyte including the observation of the first polar body (Mohr & Trounson 1984).

Semen preparation and oocyte insemination

The technique for semen preparation has been described previously (Edwards 1981; Edwards *et al.* 1981; Mahadevan & Baker 1984) and used modified Tyrode 6 medium with 50% human serum Between 50 000 and 100 000 spermatozoa were used for each oocyte insemination. This was done in a droplet of medium under sterile paraffin at 37°C in an atmosphere of 5% O_2, 5% CO_2 and 90% N_2. Insemination was performed between 4 and 5·5 h after oocyte recovery, but immature oocytes were inseminated after longer incubation (7–12 h) after recovery. Fertilization was confirmed by the presence of two pronuclei 16–20 h after insemination and subsequent cleavage of the embryo.

Assay of α_1-AT

Follicular fluid and serum α_1-AT were measured by single radial immunodiffusion (Mancini *et al.* 1965) using Nor-Partigens plate OUC103 (Hoechst Pharmaceuticals Ltd., UK). This contained monospecific rabbit and sheep antiserum to α_1-AT in agarose gel. Human plasma protein standard was also obtained from the same source.

A 5-μl sample of follicular fluid or serum was introduced individually into the wells with a Hamilton microlitre syringe. Dilutions of control plasma 1:1 (undiluted) 1:2 and 1:4 were also introduced into three wells respectively. The lids were replaced and the plates were allowed to stand at room temperature until read at 48 h to ensure that diffusion endpoint had been attained. The resulting ring precipitate diameters were measured using the Nor-Partigens measuring template. A reference curve was constructed by plotting the square of the diameters (D^2) of the control plasma precipitate ring against the known concentrations. The resulting curve intersected the ordinate between 8·5 and 13·5 mm^2 as required. This reference curve was then used to calculate the concentration of follicular and serum α_1-AT from the precipitate ring diameters observed for each sample. All

Table 1. Follicular fluid and serum alpha$_1$-antitrypsin (α_1-AT) concentrations in relation to oocyte maturity

Oocyte maturity group	n	α_1-AT levels (g/l) Follicular fluid	 Serum	Statistical analysis (P)
Immature	8	2·96 (0·22)	3·00 (0·20)	NS
Borderline mature	9	2·26 (0·17)	3·05 (0·13)	$0{\cdot}05>P>0{\cdot}02$
Mature	47	1·52 (0·06)	3·17 (0·10)	$P<0{\cdot}001$

Results are means (SE).

samples in the study were analysed in the same assay run.

Statistical analysis

Statistical analysis used Student's t-test for the comparison of means and the χ^2 test.

Results

Sixty-four of the available oocytes were scored for maturity: mature (47), borderline maturity (9) and immature (8). Eight oocytes had not been scored for maturity.

Follicular and serum α_1-AT

A comparison of the mean follicular fluid and serum α_1-AT concentrations in the three maturity groups is shown in Table 1. There was a significant difference between serum and follicular fluid α_1-AT levels in the group that yielded oocytes of borderline maturity ($0{\cdot}05 > P > 0{\cdot}22$) and this difference reached a higher degree of significance in the mature group ($P<0{\cdot}001$). There was, however, no significant difference between the serum and follicular fluid α_1-AT levels in the immature follicle group. There were no significant differences in the mean serum α_1-AT concentration between the three maturity groups but follicular fluid α_1-AT concentrations were significantly higher in the immature group compared with the mature group ($P<0{\cdot}001$) and also compared with the borderline maturity group ($0{\cdot}02> P>0{\cdot}01$).

Table 2. Follicular alpha$_1$-antitrypsin (α_1AT) and insemination outcome in eight oocytes not scored for maturity

Patient source	Follicular fluid α-AT (g/l)	Insemination outcome
A	2·00	Fertilized
A	1·80	Fertilized
A	2·25	Not fertilized
A	0·85	Fertilized
A	1·20	Fertilized
B	0·75	Fertilized
B	1·40	Fertilized
C	2·00	Not fertilized

Follicular α_1-AT and oocyte fertilization

Only 70 oocytes were analysed as two oocytes which were scored as mature and with follicular α_1-AT levels of 1·5 and 1·8 g/l were not fertilized, and non-fertilization was considered to be due to an unsatisfactory semen quality (sperm density $<3 \times 10^6$/ml and > 70% abnormal forms). Eight of the 70 analysed oocytes were unscored for maturity (Table 2). Overall 85% of the oocytes recovered from follicles with follicular fluid α_1-AT levels of $\leq 2{\cdot}0$ g/l were fertilized compared with only 25% when the α_1-AT concentration was more. This difference was highly significant ($P<0{\cdot}001$). Figure 1 shows the mean follicular α_1-AT concentration of the fertilized and unfertilized oocytes in the different maturity groups. When maturity score alone was considered, 84%, 44% and 25% of oocytes were fertilized in the mature, borderline mature and immature groups respectively. The mean follicular fluid α_1-AT concentration of the oocytes that were fertilized was significantly lower than that of the unfertilized oocytes ($0{\cdot}01 <P<0{\cdot}05$) (Fig. 2).

Discussion

An oocyte's ability to be fertilized, cleave and subsequently implant is a reflection of the matu-

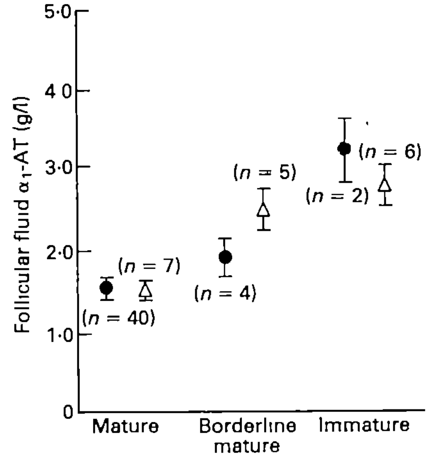

Fig. 1. Mean follicular alpha$_1$-antitrypsin (α_1-AT) of insemination outcome of different oocyte groups. Fertilized (●), unfertilized (△)

rity of the follicle from which it is recovered. Changes in follicular fluid steroid concentrations have been used as predictors of follicular maturity. High levels of follicular oestradiol in association with a rise in progesterone and a low concentration of androstenedione predict successful fertilization and cleavage for oocytes recovered from such follicles (McNatty *et al.* 1979; Carson *et al.* 1982; Trounson 1983; Fishel *et al.* 1983). Only more recently has attention been given to the possibility that other follicular fluid biochemical parameters may be of significance in assessing the quality of oocytes. Bagdasarian *et al.* (1981) suggested some function for ovarian stromal α_1-protease inhibitor in the proteolytic event of ovulation.

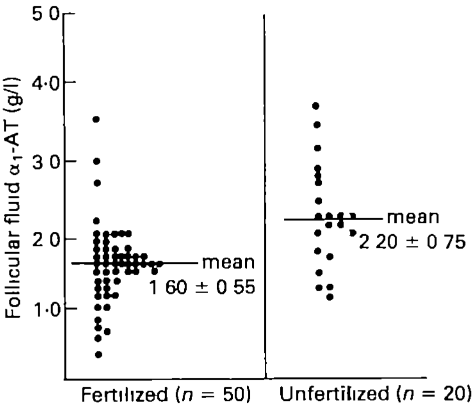

Fig. 2. Outcome of individual oocyte insemination compared with its follicular alpha$_1$-antitrypsin (α_1-AT).

Our observations show definite interfollicular differences in α_1-AT concentrations which successfully predict the maturity and ability to fertilize and cleave of oocytes recovered. Alpha$_1$-antitrypsin concentration was observed to decline with improving follicular/oocyte maturity. This observation confirms opinions, albeit indirectly, that ovulation is a proteolytic event (Beers *et al.* 1975; Strickland & Beers 1976; Carrol 1976; Espey 1980). An inverse relation between follicular fluid protease and antiprotease activity, allowing for increased protease activity as the follicle approaches maturity, ensures spontaneous ovulation. This increased protease activity probably accounts for the mucification and dispersal of the cumulus cells, a character of mature oocytes. Ovarian autodigestion under these conditions is prevented by ovarian stromal cell production of α_1-antiprotease (Bagdasarian *et al.* 1981).

Our observations are similar to those of Schumacher & Pearl (1968*a*) and Schumacher *et al.* (1972) in cervical mucus. They observed a consistent fall in cervical mucus α_1-AT during the midcycle rise of luteinizing hormone, a time when follicular and systemic oestrogens are high and systemic α_1-AT is expected to be elevated (Laurell *et al.* 1986).

Follicular α_1-AT concentration was independent of follicular fluid volume. It was more closely related to the ability of the oocyte to be fertilized which is related to the maturity. A follicular fluid α_1-AT concentration of 2 g/l appears to be the critical discrimination value between mature follicles and those of questionable maturity, this is confirmed by the high fertilization rate of 85% in oocytes from follicles with α_1-AT levels $\leq 2 \cdot 0$ g/l. This value also compares quite well with a fertilization rate of 84·4% based on maturity score alone. The highly significant difference ($P < 0 \cdot 001$) in fertilization rate between oocytes from follicles with α_1-AT concentrations above and below this critical level supports this contention.

The mechanisms involved in the maturation of oocyte and follicular rupture remain unclear. Although follicular steroid content as it pertains to oocyte and follicular maturity has been extensively studied, it is obvious that these are not the only biochemical events in this physiological phenomenon. This is supported by recent occurrences of clinical features as the unruptured luteinized follicle (Koninckx *et al.* 1980). It is possible that in such follicles the normal relation between protease and antiprotease activity is defective and hence ovulation does not occur. Attention must now be directed at other aspects of the oocyte's biochemical microenvironment other than steroids and steroidogenesis The observed changes in genital tract protease and antiprotease activity are specific physiological phenomena. They are directed at creating the optimum environment for the release, transport and union of the gametes in the female genital tract. The decrease in α_1-AT concentration in midcycle cervical mucus (Schumacher *et al.* 1977) and in follicular fluid would be in agreement with this theory.

Perhaps these events are more closely related to the phenomena of oocyte maturity ovulation and ability to be fertilized than follicular steroids as presently known. Further studies are currently being undertaken to further evaluate these observations.

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Clinical and microbiological investigation of women with acute salpingitis and their consorts

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Summary. To determine the microbiological causes of pelvic inflammatory disease, 43 women with acute salpingitis (AS) and 160 controls were studied. Amongst AS women there were significantly higher endocervical isolation rates of *Neisseria gonorrhoeae* (54% *vs* 6%), *Chlamydia trachomatis* (40% *vs* 13%), *Mycoplasma hominis* (60% *vs* 19%), enterobacteria (26% *vs* 11%) and anaerobic bacteria (58% *vs* 29%). A polymicrobial pathogenic endocervical flora was present in both gonococcal and non-gonococcal AS. Laparoscopic sampling of the fallopian tubes rarely provided useful microbiological data but did reveal the inaccuracy of clinical diagnosis of AS. Thirty-four male consorts of AS women were investigated; 20 had gonorrhoea and 27 had non-gonococcal urethritis (NGU). A high proportion of infected men had asymptomatic gonorrhoea (35%) and/or asymptomatic NGU (56%). These findings had implications for the management of AS.

The rising incidence of acute salpingitis (AS) during the past 20 years in many western countries has mirrored the increasing incidence of sexually-transmitted diseases (STD) (Cunningham 1979; Eschenbach & Holmes 1979; Eschenbach 1980). Although gonorrhoea has long been considered the major cause of AS, recent studies in Scandinavia have found a rising proportion of non-gonococcal AS, the causes of which are less well understood and the prognosis for which is worse (Paavonen *et al.* 1979; Dalaker *et al.* 1981; Moller *et al.* 1981; Gjonnaess *et al.* 1982). Investigations outside the UK making use of improved culture techniques (Mardh 1980) have indicated that *Chlamydia trachomatis*, anaerobic bacteria, enterobacteria and *Mycoplasma hominis* may contribute to the bacterial pathogenesis of AS but the relative importance of each as primary or secondary pathogens is not clear.

In the UK there has been little detailed study of AS during the past 10 years. To assess the contribution of the different microbiological causes and to determine the local pattern of AS we conducted a prospective study of women presenting with AS in Sheffield.

Patients and methods

Study population

Women of any age presenting with acute salpingitis (AS) to either the Department of Genito-Urinary Medicine or to the Gynaecology Units in Sheffield during a 2-year study period beginning June 1981 were studied.

A presumptive clinical diagnosis was made according to generally accepted criteria: i.e., the presence in women complaining of acute lower abdominal pain of one or more of the following features: fever, leucocytosis, elevated erythrocyte sedimentation rate (ESR) plus one

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or more of the following signs: adnexal tenderness, adnexal mass, cervical excitation tenderness.

The clinical diagnosis was confirmed by laparoscopy in any patient in whom there was doubt about the diagnosis or in whom a tubo-ovarian abscess was suspected. The minimal findings at laparoscopy required to confirm the clinical diagnosis were hyperaemia and oedema of the fallopian tubes. Additional confirmatory features were purulent exudate from the fimbriae or in the peritoneal cavity, the presence of hydrosalpinx or pyosalpinx, or adhesions involving the fallopian tube.

Patients who fulfilled the clinical criteria for admission into the study were subsequently excluded from analysis if they had taken any antibiotic therapy within the preceding 7 days, if other pathological conditions were found at laparoscopy to explain their abdominal pain, or if there were no features of AS observed at laparoscopy.

Controls

Two control groups were examined. One group was randomly recruited from sexually-active women presenting to the Department of Genito-Urinary Medicine with new complaints who had neither symptoms nor signs of AS. On the basis of clinical examination, these women were subdivided into those with and those without clinical evidence of lower genital tract infection.

The second group of controls was randomly selected from fertile women undergoing laparoscopic sterilization in any of the Sheffield Gynaecology Units.

Consorts

The male consorts of women presenting with AS were, wherever possible, traced and advised to attend the Department of Genito-Urinary Medicine for investigation.

Clinical assessment

For the female study population and controls, a routine clinical history was taken in which details of demographic data, gynaecological and obstetric data, sexual history and current symptoms were collected on to a standard record form. Physical examination routinely included examination of the external genitalia, abdominal palpation, vaginoscopy and bimanual pelvic examination; the findings and the patient's temperature were recorded on the forms.

For male consorts, a routine history was taken and clinical examination performed in which particular emphasis was placed upon the detection of genital abnormalities, especially the presence of urethritis.

Specimen collection

Women with AS and controls were routinely screened for sexually-transmitted diseases by microscopy and cultural examination of genital secretions. The study required the collection of additional specimens from the endocervix, which were obtained at vaginoscopy, and from the fallopian tubes in women undergoing laparoscopy. Specimen collection packs were prepared which contained in a sealable plastic bag, three cotton wool swabs and three separate 7-ml bottles of transport media:

(i) Charcoal Amies transport medium for aerobic and anaerobic bacteriology;
(ii) AN transport medium (Hafiz & McEntegart 1976) for the isolation of *Neisseria gonorrhoeae, Haemophilus ducreyi* and *Actinomyces* spp., and (in later specimens) for genital mycoplasmas.
(iii) Chlamydia transport medium (2 ml of Eagle's Minimal Essential Medium with fetal calf serum 10%, sorbitol 10%, gentamicin 20 g/ml and amphotericin B 2·5 g/ml) for the isolation of *Chlamydia trachomatis* and for virology.

Material was collected on the three cotton wool swabs from either the endocervix or the fallopian tubes and one swab was placed in each of the three transport media. Tubal specimens were obtained from the fimbrial ends of the tubes or, if they were sealed, from their serosal surface. Routine white cell count and erythrocyte sedimentation rate (ESR) were performed on peripheral venous blood collected from all women.

Specimen transportation

After collection the specimens were normally transferred to the microbiology laboratories within 2 h. In some patients who underwent emergency laparoscopy during the evening, there was a delay in receipt of specimens of up to

8 h. These specimens were usually held at room temperature before transportation.

Laboratory investigations

(i) The swab from Amies' transport medium was placed in 1 ml of proteose-peptone No 3 (Oxoid), vortex mixed for 30 s and then placed in RCM broth with paracresol (Hafiz & Oakley 1975) as enrichment for *Clostridium difficile.*

The proteose-peptone suspension was taken up in a Pasteur pipette and two drops seeded on each of the following media: blood agar, MacConkey's agar and Sabouraud's agar for aerobic incubation; blood agar with a penicillin disc, BM medium with kanamycin and metronidazole discs, Rogosa agar and CCF agar (George *et al.* 1979) for anaerobic incubation in an anaerobic cabinet (Don Whitley Scientific, Shipley, West Yorks) with an atmosphere of N_2 (80%), H_2 (10%), CO_2 (10%). All plates were incubated at 37°C for 48 h and then examined. Anaerobic cultures were reincubated for a further 48–72 h. Representatives of all colonies that grew were subcultured as necessary and identified by standard methods—aerobic and facultative species by the methods of Cowan (1974), Gram-positive anaerobes by the methods of Willis (1977) and *Bacteroides* spp. by the methods of Duerden *et al.* (1976, 1980) and Rotimi *et al.* (1981).

(ii) The swab from AN transport medium was used to inoculate clear GC selective medium (Phillips *et al.* 1972), Sheffield *H. ducreyi* medium (Kinghorn *et al.* 1982*a*), brain-heart infusion (BHI) agar and BHI with 5% horse blood (Grice & Hafiz 1983). With later specimens the swab was then placed in PPLO broth (Oxoid). GC plates were incubated at 35–36°C in CO_2 (10%) with enhanced humidity and examined after 24 and 48 h for suspected gonococcal colonies. The identity of oxidase-positive Gram-negative diplococci was confirmed by carbohydrate fermentation tests; isolates were also tested for β-lactamase production by the Nitrocefin test.

The plates of *H. ducreyi* medium were incubated at 33–34°C in CO_2 (5%) with increased humidity; they were examined after 48 h and subsequently every 24 h for 7 days for suspected *H. ducreyi* colonies. These were coherent, greenish-brown colonies that were difficult to emulsify. Gram-stained smears showed Gram-negative rods with 'school of fish' arrangement. Their identity was confirmed by positive reactions in starch aggregation and alkaline phosphatase tests and by failure to ferment carbohydrates.

BHI-agar plates were incubated anaerobically at 37°C and the BHI-blood-agar plates at 36°C in CO_2 (10%) with enhanced humidity; both were examined for typical molar-tooth-like colonies of *Actinomyces* spp. after 48 h and then every 24 h for 10 days. Suspected colonies were stained by Gram's method and identified by the results of tests for motility, aesculin hydrolysis, gelatin hydrolysis, nitrate reduction, indole production, action on milk, and fermentation of glucose, mannitol, lactose, sucrose, maltose, salicin, glycerol, xylose and arabinose.

The PPLO broth was incubated for 72 h at 37°C in air plus CO_2 (10%) and then subcultured on to a medium based upon mycoplasma medium (Oxoid CM401) and containing yeast extract (Oxoid) 25 g/l, horse serum 20 ml/80 ml of basal medium, manganese sulphate 0·2 g/l, ampicillin 1 g/l and urea 1 g/l. The plates were incubated in an anaerobic cabinet (Don Whitley Scientific, Shipley, W. Yorks) with an atmosphere of N_2 (80%), H_2 (10%), CO_2 (10%) at 37°C, and examined with a plate microscope for growth of mycoplasmas from 48 h onwards; cultures were discarded as negative after 10 days. *Mycoplasma hominis* and *Ureaplasma urealyticum* were identified by their growth appearance and fermentation reactions.

(iii) Swabs for chlamydia and virus isolations were squeezed out in the medium; the specimens were divided into three portions and stored at −70°C before tissue culture inoculation. McCoy cells, grown in Eagles MEM with fetal calf serum 10% and gentamicin, were seeded at a concentration of 2×10^5 cells/bottle into 7-ml screw capped bottles containing coverslips with 1 ml of growth medium plus cycloheximide 1 g/ml, for isolation of *C. trachomatis.* The cells were incubated for 16–18 h at 37°C in an atmosphere of air (95%) and CO_2 (5%); 0·2-ml inocula of the specimen were then seeded into duplicated bottles and centrifuged at 4500 *g* for 1 h at 37°C. The cells were incubated again for 48–72 h, after which the cover slips carrying the cells were fixed in methanol and stained with Lugol's iodine for 5 min. They were examined with a ×40 objective for inclusion bodies.

Herpesvirus hominis was isolated in human embryo lung (MRCS) or African green monkey (VERO) cell lines. Monolayers of each cell line were seeded with 0·2 ml of the specimen, incubated at 37°C for up to 14 days and observed daily for the cytopathic effect of herpes.

Investigation in male consorts

Urethral specimens were taken for microscopy and culture for *N. gonorrhoeae* and urine was examined macroscopically. From those who attended later than the presentation of their female partner with AS, urethral swabs were also taken for chlamydia culture.

Gonorrhoea was diagnosed when *N. gonorrhoeae* was isolated by culture. Non-gonococcal urethritis (NGU) was diagnosed in men when there was a urethral discharge containing ≥10 pus cells/HPF on microscopic examination (× 600 magnification) with negative smears and cultures for *N. gonorrhoeae.* It was also diagnosed in men who had been treated for gonorrhoea but in whom these clinical and microscopical abnormalities were still present 7 days after initial treatment.

Analysis of results

The epidemiological data and the microbiological findings from the endocervix and fallopian tubes in women with AS and in controls were compared with the corresponding data in contact women. Significant differences were assessed by the χ^2 tests.

Approval was given for this study by the ethics committee of the Royal Hallamshire Hospital, Sheffield.

Results

Patient numbers and diagnosis

Women with AS. Forty-five women who presented to the department of genito-urinary medicine and 20 women presenting to the gynaecology units with a clinical diagnosis of AS were admitted to the study. Laparoscopic confirmation was sought in 25 women and clinical diagnosis was confirmed in 18 (72%). An exudate from the fimbriae was seen in nine patients; smears for microscopic examination were not made because swabs were placed immediately in transport media for microbiological studies. The other seven were excluded from further analysis; three had ectopic pregnancies, two had ovarian cysts, one had pelvic endometriosis and one had no laparoscopic evidence of pelvic disease. Another 13 were excluded because they had received antibiotics within the previous 7 days and two because of unsatisfactory specimen collection. Thus, the results obtained in 43 women in whom endocervical specimens were collected were analysed; AS was confirmed by laparoscopy in 18 of them, from 15 of whom tubal specimens were collected.

Control subjects. Endocervical specimens were obtained from 45 women without clinical evidence of genital tract infection and 115 women with lower genital tract infection alone. Tubal specimens were obtained from 15 control subjects undergoing laparoscopic sterilization.

Male consorts. Thirty-four male consorts of women with AS analysed in the study were investigated, 17 of them had presented to the clinic before their female partners.

Epidemiological comparisons

In the control subjects, there were no significant epidemiological differences between the women with and those without clinical evidence of lower genital tract infection. The control groups have been combined for the comparisons with the AS group (Table 1).

There were significant differences between the groups. The mean age of women with AS (22·05 SD 5·7 years) was less than that of control women (25·4 SD 7·7 years) (P<0·002) and larger proportions of women with AS had never married and were unemployed. More women with AS admitted having had a termination of pregnancy at some time and they were less often employing any method of contraception; the difference was most marked for the oral contraceptive pill. Use of an IUCD was uncommon in both study groups. Previous episodes of pelvic inflammatory disease (PID) were significantly more frequent in this group with AS and a larger proportion had known previous episode of STD although this was not statistically significant. There were no significant differences between the groups in the number and type of recent sexual contacts. Almost all women with AS had a regular sexual partner. The proportion of each group who had previously been pregnant was similar.

Microbiology of cervical isolates

In the women with AS, there were no significant differences between those with laparoscopically

Table 1. Epidemiological comparisons

Factors in history	Number (%) of women with the given factor		Significance of differences	
	All controls (n = 160)	Women with AS (n = 43)	χ^2	P
Demographic				
Age <25 years	88 (55)	37 (86·0)	12·4	0·001
Never married	95 (59·4)	35 (81·4)	6·2	0 05
Not in employment	80 (50·0)	30 (69·8)	4·6	0·05
White European	148 (92·5)	38 (88·4)	n.s.	
Gynaecological				
<14 days since LMP	62 (38·8)	21 (48·8)	n.s.	
Never pregnant	84 (52·5)	19 (44·2)	n s	
Previous termination of pregnancy	22 (13·8)	13 (30·2)	5·4	0·05
Contraception				
Hormonal	93 (58·1)	13 (30·3)	10·6	0·02
IUCD	9 (5·6)	4 (9·3)		
Barrier	6 (3·8)	3 (7·0)		
None	52 (32·5)	23 (53·5)		
Sexual history				
Past history of STD	55 (34·3)	19 (44·2)	n.s.	
Past history of PID	8 (5·0)	12 (27·2)	17·5	0.001
>1 consort in preceding 8 weeks	28 (17·5)	8 (18·7)	n.s.	
Regular consorts	144 (90·0)	41 (95·0)	n.s	
Casual consorts	26 (16·3)	9 (21·0)	n s	

LMP, Last menstrual period; IUCD, intrauterine contraceptive device; STD, sexually-transmitted disease; PID; pelvic inflammatory disease.

confirmed tubal infection and those where the diagnosis was solely clinical. A comparison of the endocervical isolates from women with AS and from controls with no clinical infection or with lower genital tract infection is shown in Table 2.

Of the aerobic bacterial species there were significantly increased isolation rates in women with AS for *N. gonorrhoeae* (54% *vs* 6%), enterobacteria (26% *vs* 10%) and *H. ducreyi* (16% *vs* 5%).

Of the anaerobic bacterial species, there were significantly increased isolation rates in women with AS for *B. bivius* (28% *vs* 9%), *B. disiens* (19% *vs* 12%), *B. melaninogenicus* ss. *melaninogenicus* (14% *vs* 1%), and anaerobic cocci (30% *vs* 16%). Overall, *Bacteroides* spp. of the melaninogenicus-oralis group and/or anaerobic cocci were isolated from 58% of the women with AS but from only 29% of the controls. There were no significant differences in the isolation rates of the asaccharolytic or fragilis groups of *Bacteroides* between women with AS and controls.

C. trachomatis was isolated from 17 (40%) women with AS but from only 21 (13%) controls (P<0·001). There were no significant differences in the endocervical isolation rates for herpesvirus hominis or other viruses between the groups.

During the course of the study, a culture technique was introduced for the isolation of *Actinomyces* spp. The results of valid cultures are shown in Table 3. No significant difference was found between the isolation rates in women with AS and controls.

Initially methods for the isolation of genital mycoplasmas were inappropriate and insensitive. Suitable methods were introduced during the course of the study and the results of valid cultures are shown in Table 4. There was a significantly increased isolation rate for *M. hominis* (60%) from women with AS (P<0·001), but not for *U. urealyticum* (20%).

The endocervical isolation rates for the dif-

Table 2. Microbiological findings in endocervical canal

Species isolated	Number (%) colonised by the given species in subjects with			Significance of differences	
	No clinical infection ($n = 45$)	Lower genital tract infection ($n = 115$)	AS ($n = 43$)	χ^2_2	P
Aerobic and facultative bacteria					
N. gonorrhoeae	—	10 (8·7)	23 (53·5)	57·4	<0·00
Other *Neisseria* spp.	—	3 (2·6)	1 (2·3)	n.s.	
Streptococci					
α-haemolytic	7 (15·6)	16 (13·9)	7 (16·3)	n.s.	
β-haemolytic	—	2 (1·7)	1 (2·3)	n.s.	
Str. faecalis	5 (11·1)	19 (16·5)	9 (20·9)	n.s	
Staphylococci					
S. aureus	—	2 (1·7)	—	n.s.	
coagulase negative	16 (35·6)	38 (33·0)	20 (46·5)	n.s.	
Lactobacilli	27 (60·0)	54 (47·0)	11 (25·6)	10·8	<0·01
Coryneforms	11 (24·4)	42 (36·5)	25 (58·1)	11·0	<0·01
Gardnerella vaginalis	3 (6·7)	23 (20·0)	10 (23·3)	n.s.	
Enterobacteria					
E. coli	2 (4·4)	13 (11·3)	7 (16·3)	n.s.	
Proteus spp.	1 (2·2)	1	2 (4·7)	n.s.	
Klebsiella spp.	—	—	2 (4·7)	n.s.	
H. ducreyi	1 (2·2)	7 (6.1)	7 (16·3)	7·0	<0·05
Candida spp.	3 (6·7)	20 (17·4)	4 (9·3)	n.s.	
Anaerobic bacteria					
B. bivius	2 (4·4)	13 (11·3)	12 (27·9)	11·6	<0·01
B. disiens	—	19 (16·5)	8 (18·6)	9·0	<0·05
B. oralis	1 (2·2)	12 (10·4)	7 (16·3)	n.s.	
B. melaninogenicus ss. *melaninogenicus*	—	1 (0·9)	6 (14·0)	14·4	<0·01
B. melaninogenicus ss. *intermedius*	—	6 (5·2)	1 (2·3)	n.s.	
B. asaccharolyticus	—	8 (7·0)	3 (7·0)	n.s.	
B. ureolyticus	—	1 (0·9)	1 (2·3)	n.s.	
B. fragilis	—	—	2 (4·7)	n.s.	
Fusobacteria	—	2 (1·7)	2 (4·7)	n.s.	
Anaerobic cocci	1 (2·2)	24 (20·9)	13 (30·2)	12·2	<0·01
Veillonellae	—	3 (2·6)	—	n.s.	
Clostridia	—	1 (0·9)	—	n.s.	
Chlamydia trachomatis	1 (2·2)	20 (17·4)	17 (39·5)	20·4	<0·001
Herpesvirus hominis	2 (4·4)	4 (3·5)	1 (2·3)	n.s.	
Other viruses	1 (2·2)	—	—	n.s.	

ferent microbial species in patients with *N. gonorrhoeae*-associated AS and non-gonococcal AS are compared in Table 5. There were no significant differences between the findings in the two groups of patients.

Microbiological isolates from the fallopian tubes

In the 15 control women undergoing laparoscopic tubal ligation, no growth was found on bacteriological, chlamydial or viral culture of tubal swabs from 10 (66·7%), coagulase-negative staphylococci were found in four and a *Candida* sp. was isolated from one woman; the isolates were probably skin contaminants.

The results of culture of tubal specimens from women with AS were disappointing. *N. gonorrhoeae* was isolated from the fallopian tubes in three of five women (60%) from whom it was isolated from the endocervix; no other organisms were isolated from these women. Of the 10

Table 3. Isolation of *Actinomyces* spp from endocervical canal

Subject group	Number of women tested	Number (%) of women from whom *Actinomyces* spp. were isolated
No clinical infection	23	6 (26·1)
Lower genital tract infection	70	15 (21·4)
Acute salpingitis	31	3 (9·7)*

* $\chi^2_2 = 2{\cdot}7, P{>}0{\cdot}1$.

women with non-gonococcal AS, no growth was obtained from five. Coagulase-negative staphylococci, coryneforms or *Candida* spp. were found in three women without other significant pathogens and were, again, probably contaminants. Anaerobic bacteria were isolated from two women with tubo-ovarian abscesses. *B. fragilis* and *Fusobacterium necrophorum* were isolated with an α-haemolytic streptococcus from the first and *B. melaninogenicus* ss. *melaninogenicus, F. polymorphum* and anaerobic cocci from the second. No bacteria were isolated from the fallopian tubes when the fimbrial ends were fused unless there was free pus in the peritoneal cavity.

Chlamydia, viruses and mycoplasmas were not isolated from the fallopian tubes of any woman.

Investigations in male consorts of women with AS

The results of cultures performed on male consorts are shown in Table 6. Of the 34 men investigated, 20 had urethral gonorrhoea which was asymptomatic in 7 (35%). NGU occurred in 27 men (10 had NGU alone, 17 had postgonococcal urethritis) of whom 15 (56%) were without symptoms. Only four men, each of whom was a consort of a woman with non-gonococcal PID, were free of either gonorrhoea or NGU when examined.

Discussion

Diagnostic aspects

In this study AS was confirmed as the cause of pelvic pain in 18 (72%) of 25 women examined by laparoscopy. This finding is compatible with those of Westrom (1980), since confirmed by others (Ledger 1980; Bartisch & Dillon 1981; Hein *et al.* 1981), that in up to one third of women with the clinical features of AS the diagnosis cannot be confirmed at laparoscopy. The accuracy of clinical diagnosis improves when severe manifestations such as adnexal mass or peritonitis are present. We could not obtain laparoscopic confirmation of all women with AS for various reasons including patients refusing hospital admission and difficulties in making theatre time immediately available. In many cases insistence upon laparoscopy would have delayed antibiotic therapy in ill patients in whom pathogens had already been demonstrated by microscopy in endocervical specimens. We have, therefore, included in our analysis 25 women with AS in whom laparoscopy was not performed to provide data on an unselected population. Although comparison of their epidemiological and microbiological data showed no significant differences from those of the 18 women with laparoscopically confirmed AS, the results from the combined group should be interpreted with caution.

Epidemiological observations

We identified young, never married and unemployed women, especially those with known

Table 4. Isolation of genital mycoplasmas from endocervical canal

Subject group	Number of women tested	Number (%) from whom *U urealyticum* was isolated	Number (%) from whom *M hominis* was isolated
No clinical infection	14	1 (7·7)	0
Lower genital tract infection	45	10 (22·2)	16 (35·6)
Acute salpingitis	20	4 (20·0)	12 (60·0)*

* $\chi^2_2 = 12{\cdot}8$; $P{<}0{\cdot}001$

Table 5. Comparison of endocervical isolates in gonococcal and non-gonococcal acute salpingitis (AS)

	Number (%) of women colonized by the given species	
Species isolated	Gonococcal AS (n = 23)	Non-gonococcal AS (n = 20)
Enterobacteria	5 (22)	6 (30)
H ducreyi	5 (22)	2 (10)
Bacteroides spp. and anaerobic cocci	12 (53)	13 (65)
C. trachomatis	9 (39)	8 (40)
M hominis	6/9 (66)	6/11 (55)

preceding episodes of AS, as being at higher risk of AS. Previous therapeutic termination of pregnancy, which had been performed within 6 weeks of presentation in only one patient, was another risk factor. It is uncertain whether this observation relates to possible damage to cervical defence mechanisms or unwanted pregnancy having the same epidemiology as sexually transmitted diseases. Use of effective contraception, especially hormonal, was significantly less common in AS women than in controls. IUCD usage was rare in both groups

These observations are largely in accordance with the independent variables identified as indicators of AS risk in other studies (Hager & Wiesner 1979; Sweet *et al.* 1981; Shafer *et al.* 1982). Westrom (1980) found that women with earlier sexual debut were more likely to have multiple sexual partners and more prone to acquire the sexually transmitted pathogens that initiate AS. The risks were increased in those with a past history of uncomplicated gonorrhoea or other STD. At least one quarter of women who suffered one episode of AS will experience further attacks. Contraceptive method also influences the risk (Eschenbach *et al.* 1977, Flesh *et al.* 1979; Kelaghan *et al.* 1982), oral contraceptive usage appears to provide some protective effect whereas use of the IUCD has been found to increase the risk. Although the risk of AS increases with the number of sexual partners, we found no significant differences between AS women and controls in number and type of recent sexual relations. The observation that almost all AS women had continuing relations with men who were a likely source of reinfection unless they were simultaneously investigated and, where necessary, treated is important.

Microbiological aspects

The traditional subdivision of AS into gonococcal and non-gonococcal types depends upon the results of endocervical culture for *N. gonorrhoeae*. It is estimated that 7–10% of all gonococcal infections in women are complicated by AS. There are wide geographic variations in the proportion of all AS cases which are

Table 6. Investigations of male consorts of women with acute salpingitis (AS)

		Number of consorts with						
		Gonorrhoea			NGU			
Groups of men	Number investigated	Symptomatic	Asymptomatic	Total	Symptomatic	Asymptomatic	Total	Neither gonorrhoea nor NGU
Consorts of women with gonococcal AS (n = 23)	20	12	6	18 (90·0%)	6	11	17 (85·0%)	0
Consorts of women with non-gonococcal AS (n = 20)	14	1	1	2 (14·3%)	6	4	10 (71·4%)	4 (28·6%)
Total	34	13	7	20 (58·9%)	12	15	27 (79·4%)	4 (11·8%)

NGU, non-gonococcal urethritis

gonococcal: 70–80% in inner city women in the USA, 40–50% in other USA populations and only 10–20% in Nordic populations (Eschenbach *et al.* 1977; Cunningham *et al.* 1978; Chow *et al.* 1979; Bowie & Jones 1981). *N. gonorrhoeae* is the most frequent tubal isolate from AS women with endocervical gonorrhoea although it can be cultured from the tubes in only about one third of cases.

Our findings of endocervical gonorrhoea in 54% of the AS women, significantly more than in controls, and from 3 of 5 tubal specimens from AS women with endocervical gonorrhoea are compatible with these observations from earlier studies. However, we frequently isolated other STD or opportunist pathogens from endocervical specimens in these women which suggests that the polymicrobial aetiology of gonococcal AS must be considered in therapeutic regimens.

Many recent studies have shown that non-gonococcal AS responds less well to penicillin, cephalosporins or spectinomycin, is more often 'silent' and has a worse prognosis than gonococcal AS.

Considerable attention has been devoted to *C. trachomatis*, an important cause of genital tract disease in men and women and of neonatal infection. There is overwhelming evidence for the role of *C. trachomatis* in the pathogenesis of AS from cultural and serological studies in women with AS or infertility due to distal tubal disease as well as from animal models (Henry-Suchet *et al.* 1980; Mardh *et al.* 1981*a,b*; Svensson *et al.* 1981; Gjonnaess *et al.* 1982; Moore *et al.* 1982; Osser & Persson 1982; Wolner-Hannsen *et al* 1982). In Scandinavia, *C. trachomatis* has been isolated from 40% of cases. In addition, Paavonen *et al.* (1981) found that 18% of 50 AS women who were culture-negative for *C. trachomatis* seroconverted.

We also isolated *C. trachomatis* from 40% of AS women, significantly more often than from controls and with equal frequency from patients with gonococcal and non-gonococcal AS. In a subsequent investigation we have found that six (23%) of 26 AS women who were *C. trachomatis* culture-negative either had very high serum levels of antichlamydial IgC antibody at presentation or were shown to seroconvert. These observations suggest that *C. trachomatis* may have played a role in the pathogenesis of AS in about 60% of our patients. We suggest that both cultural and serological evidence of chlamydial infection should be sought routinely in women presenting with AS.

Genital mycoplasmas are normal inhabitants of the genital tract whose presence may correlate with an individual's sexual experience rather than with the presence of disease. Experimental infection of primates with *M. hominis* leads to adnexal perilymphatic inflammation without tubal occlusion and the organism has been implicated as the cause of AS in several studies (Mardh & Westrom 1970; Stray-Pedersen *et al.* 1978; Moller *et al.* 1981). It has been isolated from the fallopian tubes of 2–20% of AS women and serological evidence of current infection has been found in 12–32% of cases. *U. urealyticum* has been isolated from the fallopian tubes of 17% of AS women (Henry-Suchet *et al.* 1980), although most studies have failed to demonstrate any significant difference in endocervical isolation rates between AS women and controls. We found significantly increased endocervical isolation rates of *M. hominis*, but not of *U urealyticum*, from AS women, especially from those with associated gonorrhoea.

Thompson *et al.* (1980) isolated enterobacteria from the peritoneal cavity in 17% of AS women and Nilsson *et al.* (1981) found them to be associated with endometritis in IUCD users. Serological evidence for their role in AS has been provided by Paavonen *et al.* (1981) who found that one third of AS women had significant rises in antibody titres to enterobacterial common antigen. In our study, despite few IUCD users, we found significantly increased endocervical isolation rates from AS women. Enterobacteria may be primary pathogens in IUCD users and secondary pathogens in women with other initiating STD.

H. ducreyi causes chancroid and may be isolated from genital ulcers in association with other STD (Kinghorn *et al.* 1982*b*). Using improved culture methods, we found a higher endocervical isolation rate from AS women than from controls, which may relate to their greater incidence of other STD and also confirms the hypothesis that *H. ducreyi* can colonize the female genital tract in the absence of genital ulceration. This organism has not been implicated in PID by any previous workers and any relation with the pathogenesis of AS requires further investigation.

Non-sporing anaerobic bacteria are isolated from virtually all pelvic abscesses and are also common in AS of 48 h duration. The results of anaerobic culture depend upon the quality of cultural techniques (Monif & Baer 1982). The role of *B. fragilis*, which is not a genital tract commensal, in AS is disputed (Soderberg *et al.* 1979) although Paavonen *et al.* (1981) found that one third of AS women had a significant rise in antibody titre to the capsular polysaccharide of *B. fragilis*, irrespective of whether *N. gonorrhoeae* or *C. trachomatis* were also isolated. Peptococci or peptostreptococci have been isolated from 20–60% of women with polymicrobial AS. We found anaerobic bacteria, especially *Bacteroides* of the melaninogenicus-oralis group and anaerobic cocci, in endocervical specimens from most AS women, especially in those with non-gonococcal AS, and in two tubal specimens. Our endocervical findings may simply reflect a higher proportion of AS women with bacterial (anaerobe-associated) vaginosis. Further investigation of whether women with bacterial vaginosis are at increased risk of developing AS is desirable.

Proof that any of the bacteria isolated in this study were directly involved in the disease could come only from their isolation from the tubes themselves. There were few direct isolations because to be more invasive would not have been ethical. If the tubes were sealed, or there was no exudate to sample, only the outer surface of the inflamed tubes could be swabbed and this was unlikely to yield bacteria. Sampling the sites of infection (the tubal lumen) would have required puncture of the tube, which was not considered to be an appropriate or a clinically necessary investigation.

Findings in male consorts

There have been few comprehensive studies in the male consorts of AS women (Handsfield *et al.* 1974; Gilstrap *et al.* 1977; McCormack *et al.* 1979; Volkin *et al.* 1979). Contact tracing has shown that 39–83% of consorts of women with gonococcal AS have gonorrhoea and many of these infections are asymptomatic (32–64%). Women who have had AS and have an untreated asymptomatic consort have a high-risk of reinfection. Only four of the 34 male consorts in our study had no urethral infection; 20 had gonorrhoea, of whom 35% were asymptomatic, and 27 had non-gonococcal urethritis, of whom 55% were asymptomatic. This indicates that male consorts of all AS women should be routinely investigated by a genito-urinary physician irrespective of whether symptoms are present or of the microbiological findings in the women.

Therapeutic implications

Although laparoscopic sampling of the fallopian tubes usually failed to provide useful microbiological data to guide therapy, it did confirm the inaccuracy of clinical diagnosis of AS and the desirability of routine laparoscopy to exclude other causes of pelvic pain.

But the finding of a varied polymicrobial endocervical flora in women with gonococcal and with non-gonococcal AS indicates that AS is a complex infection and that single drug regimens are unlikely to be successful in eradicating all potential pathogens. Combination therapy should routinely include antibiotics active against *C. trachomatis* and *M. hominis* and anaerobic bacteria as well as against *N. gonorrhoeae*.

Sexually-transmitted pathogens most commonly initiate AS. Prevention of AS and its sequelae demands good clinical, epidemiological and diagnostic facilities so that early infections in women and their consorts are diagnosed and treated before spontaneous or iatrogenic ascent to the fallopian tubes occurs.

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Fetal heart rate pattern during decompression of a hydrocephalic head. Case report

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Case report

A 23-year-old primigravida, at approximately 40 weeks gestation, was admitted to the Soroka Medical Centre delivery room in active labour. Her past medical and family history were unremarkable and according to her, the present pregnancy had been uneventful. She had not attended for antenatal care and was seen for the first time by an obstetrician in the delivery room.

On admission, her blood pressure was 110/70 mmHg with a regular pulse rate of 80/min. General physical examination revealed no abnormalities. The uterine height was 43 cm, she had a singleton fetus in vertex presentation, with the head high above the pubic brim. An ultrasound scan demonstrated a hydrocephalic fetal head with a biparietal diameter of 11·4 cm and brain cortex thickness of 0·6 cm. The cervix was fully effaced and 8 cm dilated.

External monitoring recorded regular uterine contractions and an internal scalp electrode registered baseline bradycardia with normal baseline variability (Fig. 1A). To enable vaginal delivery, transabdominal puncture of the hydrocephalic head was performed and under ultrasonic guidance, 400 ml of cerebrospinal fluid was drained.

During the decompression, the fetal heart rate was monitored continuously and Fig. 1B shows the fetal heart rate pattern after drainage of cerebrospinal fluid. Baseline heart rate changed from severe to moderate bradycardia. Shortly thereafter the patient was delivered spontaneously of a stillborn 3·8 kg male infant. The post mortem diagnosis was severe hydrocephalus with no other concomitant malformation.

Comment

The normal fetal heart rate pattern is the result of interaction between the sympathetic and parasympathetic components of the autonomic nervous system (Renou *et al.* 1969). Elevated intracranial pressure (head compression) has been found to cause persistent baseline bradycardia (Mocsary *et al.* 1970; Young & Weinstein 1976). It is therefore consistent that elevated intracranial pressure caused severe baseline bradycardia in the present case The drainage of cerebrospinal fluid caused a dramatic shift from overtly abnormal to normal fetal heart rate pattern. This provides convincing evidence that intracranial pressure plays a critical role in the pathophysiology of fetal heart rate patterns.

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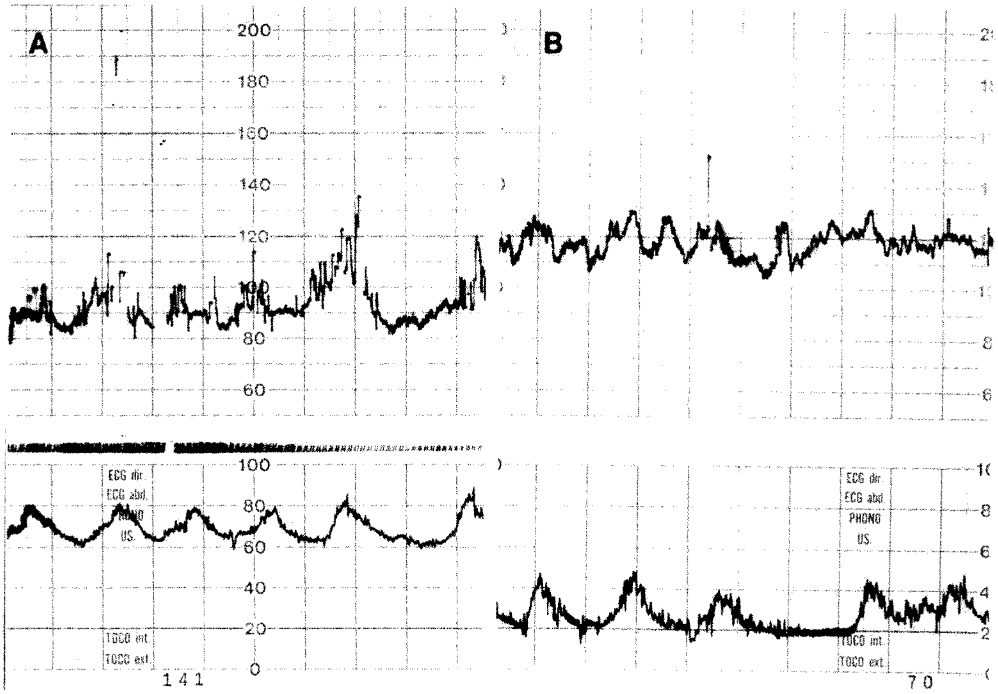

Fig. 1. Cardiotocograph showing (A) bradycardia with normal variability before puncture and (B) rise of basal heart rate with normal variability after drainage of 400 ml of cerebrospinal fluid.

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Incarceration of the retroverted gravid uterus at term. Case report

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Case report

The patient was a 20-year-old Asian who was pregnant for the third time. Her first pregnancy had ended as a spontaneous abortion at 24 weeks gestation. The second pregnancy was complicated by a major placenta praevia and a healthy 2·54 kg infant was born at 38 weeks by elective lower segment caesarean section, at which time the uterus was found to be bicornuate. No other pelvic anomalies were noted.

After a threatened abortion at 6 weeks, the third pregnancy progressed normally There were no antenatal urinary or alimentary symptoms. Labour began at 37 weeks gestation. On abdominal examination, a single fetus was noted with the head deeply engaged in the pelvis. Vaginal examination confirmed that the head was deep in the pelvis but behind the posterior vaginal wall. The cervix was not easily reached but was thought to be markedly anterior and very high. The membranes were intact

Labour was allowed to continue but after 6 hours of regular contractions the vaginal findings were unchanged. External monitoring of the fetal heart rate showed a mild tachycardia (good baseline variability) but no decelerations

A diagnosis of possible sacculation/incarceration of the uterus was made and the patient was examined under anaesthesia. With difficulty, the cervix was found to be anterior to the fetus, at the level of the umbilicus, and with a breech 'presentation' (Fig. 1). The decision was therefore made to perform a caesarean section To facilitate the access to the fetus at operation, an attempt was made to correct the uterine retroversion by gentle pressure upwards on the fetal head deeply engaged in the pelvis. This manoeuvre was accomplished with surprisingly little difficulty, the uterus becoming anteverted with the fetus now assuming a transverse lie.

Lower segment caesarean section was then performed without difficulty A live 2·86 kg male infant was born in good condition. The uterus was bicornuate. The anterior lower uterine segment was considerably stretched and thinned (Fig. 2). The previous section scar was intact

The puerperium was uneventful. A subsequent hysterosalpingogram confirmed a bicornuate uterus remaining in retroversion but with no residual sacculation.

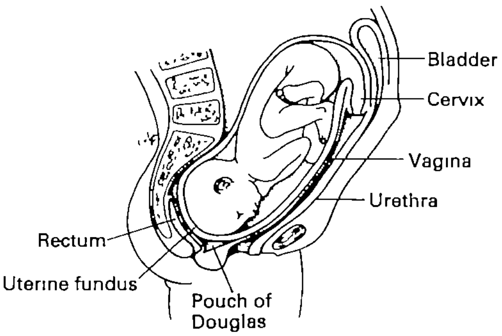

Fig. 1. Incarceration of the retroverted gravid uterus at term.

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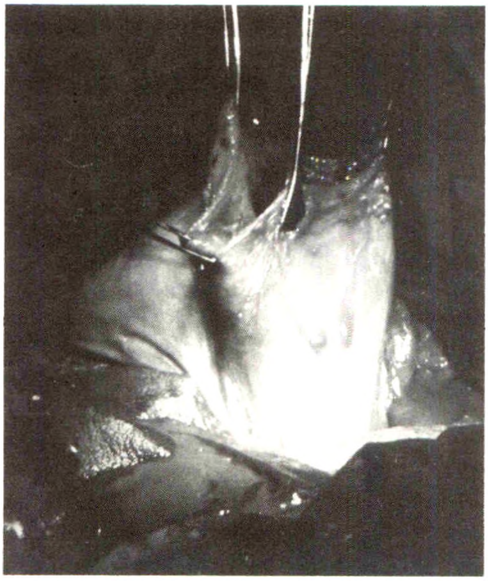

Fig. 2. Considerably attenuated anterior lower segment. The transverse lower segment incision is marked by 4 Green Armytage clamps and was made through the old scar. Behind this can be seen the body of the uterus.

Discussion

Incarceration of the retroverted gravid uterus in the second trimester is said to occur in 1 in 3000 deliveries. The associated symptoms of bowel and bladder dysfunction are well recognized (Hunter 1776; Gibbons & Paley 1969). However, incarceration of the retroverted gravid uterus presenting as late as the third trimester has been reported on only six occasions (Merriman 1806; Oldham 1860; Maiss von Arch 1899; Murray 1934; Smith *et al.* 1962; Wood 1967). In such cases, the uterine fundus becomes incarcerated in the pelvic cavity with the result that the anterior uterine wall becomes grossly stretched to accommodate the developing pregnancy. Such 'sacculation' of the anterior uterine wall is often confused with, but must be distinguished from, true uterine sacculation. The latter may be defined as a diffuse ballooning of some portion of the uterine wall in a uterus of normal polarity.

In true sacculation, the aetiology of which is unknown, the condition is often symptomless and is sometimes only diagnosed in labour by the finding of a mass alongside the uterine body which may or may not contain either fetal parts or the placenta. As the polarity of the uterus is normal, labour may at times proceed normally and operative delivery is not always a necessity (Weissberg & Gall 1972).

With incarceration of the retroverted uterus in the third trimester, the patient may give a history of lower abdominal pain or micturition problems or, as in our case, may be symptomless and the problem only discovered in labour. Due to the disordered polarity of the uterus, with the fundus in the pelvis, the contractions will fail to dilate the cervix effectively. Rupture of the uterus is a distinct possibility and has been recorded (Maiss von Arch 1899).

The reason for the persistent retroversion of the gravid uterus in late pregnancy has, in other cases, been due to the presence of pelvic adhesions (Murray 1934), an impacted fundal fibroid (Smith *et al.* 1962) or a double uterus (Wood 1967). A deep sacral concavity with an overlying sacral promontory has also been suggested as a possible aetiological factor. Our patient resembles the one described by Wood (1967) in that a congential uterine abnormality was present. Most cases occur in primigravidae but in one case which necessitated a hysterotomy at 27 weeks, the patient had had a previous normal vaginal delivery (Fadel & Misenhimer 1974).

The diagnosis was suspected in our patient during labour. The finding of a mass deep in the pelvis behind the posterior vaginal wall with the cervix displaced markedly forwards and above the symphysis pubis is typical. However, pelvic findings can be misleading, particularly if there is no tangible fetal pole present in the pelvic uterine fundus. Ultrasound scan would, undoubtedly, nowadays be a useful method of distinguishing this condition from such other problems as cervical fibroids, pelvic ovarian cysts etc. which make up the differential diagnoses.

Rupture of the uterus is a serious potential complication if labour is allowed to continue (Maiss von Arch 1899). The two occasions when a vaginal delivery was achieved took place in the days before the advent of safe lower segment caesarean section and in both cases the infant was born dead (Merriman 1806; Oldham 1860). But whereas operative delivery is nowadays advisable, problems have been incurred in other cases both in negotiating the cranially displaced bladder as well as in placing the uterine incision so low as to involve the cervical canal. To facilitate the caesarean section we therefore attempted to push the fetal head up out of the pelvis at the time of the EUA. Whilst this was done with surprising ease and made the subsequent caesarean section much easier, it could have threatened the integrity of the lower segment that was already compromised by the previous section.

Wood (1967) reported the only patient who has had an incarceration of the uterus in the third trimester in two successive pregnancies. Hysterosalpingogram in our patient has subsequently shown that the bicornuate uterus is still retroverted. The problem therefore could possibly recur with any future pregnancy. It might have been advisable for us to have tried to correct the retroversion surgically at the time of caesarean section. However, as pointed out by Fadel & Misenhimer (1974), such corrective measures may not be successful under such circumstances and it is probably far better to see the patient early in the next pregnancy when, if necessary, a Hodge pessary can be inserted to maintain the uterus in anteversion during the early weeks of pregnancy.

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Intraepithelial neoplasia arising in an artificial vagina. Case report

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Case report

A 17-year-old girl presented in 1972, 6 months after her marriage, with lack of menstruation. Examination under anaesthesia revealed absent vagina and uterus. A McIndoe reconstruction was therefore performed and a vaginal mould used postoperatively to keep the vagina open. Three months after her operation, she was unable to replace the mould and, on examination, there was a ring stricture just below the vault. The vagina, however, was considered adequate for intercourse. She was then not seen for 12 years until 1984 when she presented with progressive dyspareunia and vaginal stenosis.

On examination the vaginal opening was seen to be adequate and the vagina had a depth of 7 cm but the posterior wall of the vagina was noticed to be very thin. There were granulations at the vault of the vagina from which a small biopsy was taken and initially reported as being squamous carcinoma but it was not possible to assess invasion because of the smallness and poor orientation of the biopsy fragment. Cytology was not helpful as the smears taken consisted of degenerate and anucleated squamous cells only.

Because of the histology, the patient was colposcoped and nine punch biopsies were taken under general anaesthesia, one from the raw area already biopsied, one from a smaller lesion adjacent to this and the others randomly from aceto-white areas. Histology of the lesions showed intraepithelial neoplasia affecting the full thickness of the epithelium (Grade 3) but with no invasion (Fig. 1). All other biopsies showed koilocytosis and occasional dyskeratosis suggesting human papillomavirus (HPV) infection (Fig. 2). The original skin graft was therefore replaced but only after a rather difficult dissection. The whole of the original vaginoplasty was submitted for histology. Macroscopically the only lesions identifiable were the biopsy sites. Random blocks taken throughout showed koilocytosis only, with no evidence of neoplasia.

The skin graft took well but subsequently there were several episodes of anaerobic infection. The patient was seen a few months postoperatively when colposcopy revealed a capacious vagina, again covered with flat warts. Punch biopsies taken showed changes indicative of HPV infection but vaginal smears consisted of keratinous debris only. At 6 months the histological appearances were still suggestive of HPV infection but the features thought to amount to intraepithelial neoplasia (Grade 1). The vaginal smear taken at this visit contained one group of hyperkeratotic atypical squamous cells. Material was submitted for identification of HPV by DNA hybridization techniques but no virus could be identified (this technique had not been available earlier).

Discussion

There have been three previously reported cases of squamous cell carcinoma in skin graft reconstructions of artificial vaginas in the world literature (Jackson 1959; Duckler 1972; Rotmensch *et al.* 1983) and one case has been diagnosed in Britain this year (J. R. H. Pinkerton, personal communication). We have not found intraepithelial neoplasia previously reported or any reports of HPV infection. Many authors have now cited the association between cervical cancer and its precursors and HPV infection,

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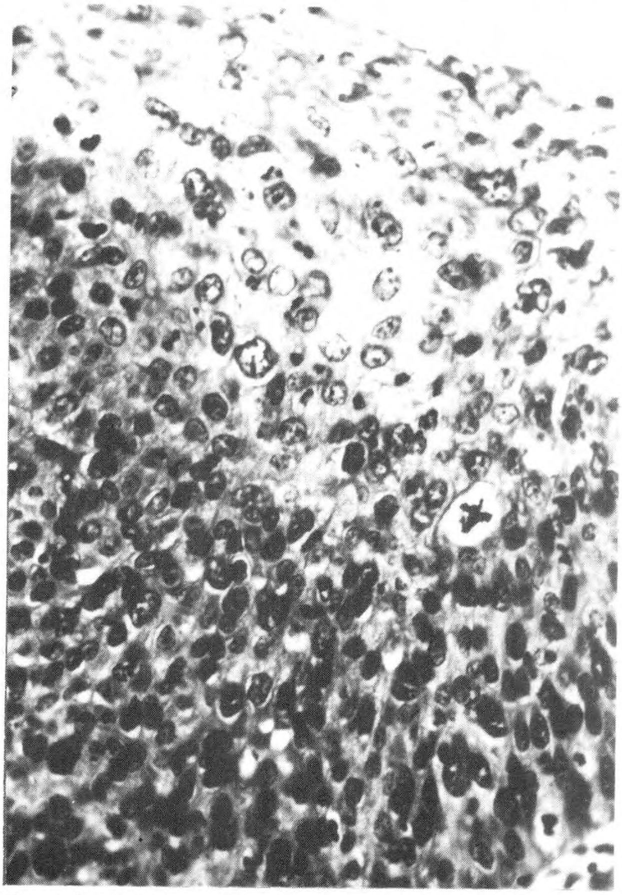

Fig. 1. Vaginal biopsy showing intraepithelial neoplasia affecting the full thickness of the epithelium. (VaIN 3).

whether causal or casual. Papillomaviruses are known to be carcinogenic in other sites and species, usually in association with a cofactor. For example, papillomas in the oesophagus or intestines of cows caused by bovine papillomavirus 4 progress to carcinoma in the presence of bracken which acts as a cofactor (Jarrett 1981). If HPV is carcinogenic in the genital tract, one of the most probable agents acting with it is herpes simplex virus (HSV) which may act as an initiator or a cofactor (zur Hausen 1982). Recent work using DNA hybridization techniques has shown different subtypes of HPV associated with various cervical lesions. Four main subtypes are recognized in the genital tract, the associations being types 6 and 11 with genital warts and types 16 and 18 with cervical cancer (Coleman & Richman 1985). Type 16 has been identified in cases of CIN considered to have a high risk of progression to carcinoma because of the presence of abnormal mitoses (Crum *et al.* 1985). It now seems possible that, at some time in the future by using DNA probes, we may be able to separate those forms of CIN more likely to progress from those associated with non-carcinogenic subtypes. With the concept of the lower genital tract as a continuum it may be extrapolated to similar lesions in the vagina and vulva. In this patient the epithelium is not of genital origin but from a split skin graft of the thigh but appears to respond as genital epithelium in as much as it has shown features of HPV infection and of intraepithelial neoplasia. The features of HPV infection persist in our patient despite the biopsy examined by hybridization showing no HPV particles present and in view of this we will have to repeat DNA hybridization techniques at a later date. Careful monitoring by colposcopy and appropriate sampling will be essential in this patient, but identification of a papilloma subtype

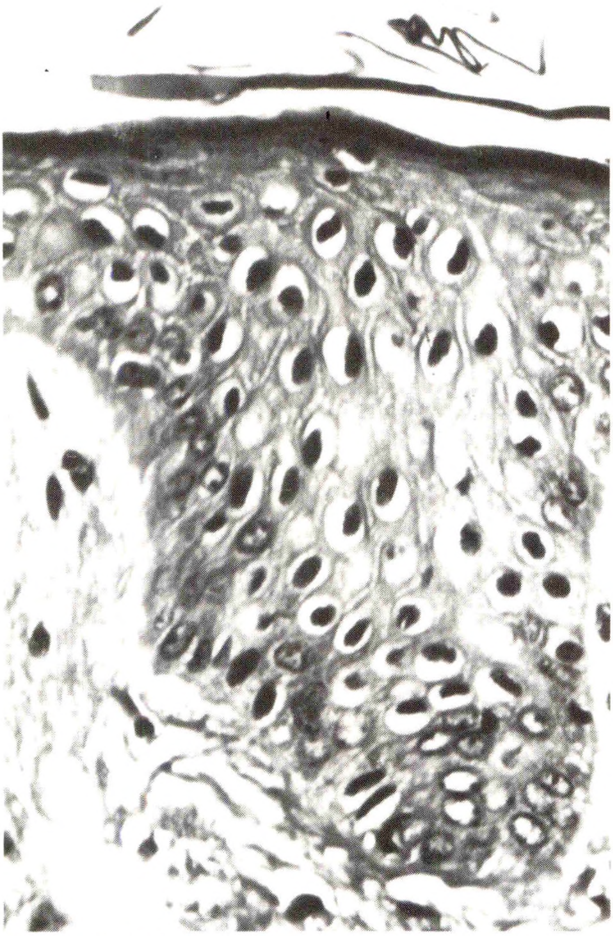

Fig. 2. Vaginal biopsy showing koilocytosis suggestive of papillomavirus infection.

with higher malignant potential may warrant a more aggressive approach.

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting in January 1986 at the Royal College of Obstetricians and Gynaecologists

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Secretory proteins of the endometrium and decidua. Studies on pregnancy-associated endometrial α_1- and α_2-globulin (α_1- and α_2-PEG) by J. O. Drife* & S C. Bell†. Departments of *Obstetrics and Gynaecology and †Biochemistry, University of Leicester, PO Box 65, Leicester LE2 7LX

We have identified five major secretory proteins whose in-vitro synthesis and secretion by the endometrium show quantitative changes during the menstrual cycle. Endometrial protein (EP)13 with molecular radius (M_r) of 33 kD, EP15 (M_r 28 kD) and EP14 (M_r 32 kD) had maximal rates of synthesis and secretion during the follicular, mid- to late luteal, and late luteal phases respectively, and were unaffected by short-term progesterone exposure *in vitro* By contrast, synthesis and secretion of EP9 (M_r 54 kD) and EP11 (M_r 45 kD) were decreased and increased respectively by short-term exposure to progesterone *in vitro*, irrespective of the stage of the cycle. The results support the contention that EP15 (α_2-PEG), the major secretory protein product of first trimester pregnancy endometrium, is derived from the secretory endometrium, and EP14 (α_1-PEG), the major product of the second and third trimester pregnancy endometrium, is derived from decidualized endometrium. They also suggest that synthesis and secretion of these two major products is not dependent upon the presence of the fetoplacental unit but is related primarily to the progesterone-dependent differentiation of the endometrium. Monospecific polyclonal antisera raised against these proteins have been used in a rocket immunoelectrophoretic assay. During pregnancy highest levels of EP15 (α_2-PEG) and EP14 (α_1-PEG) are detectable in amniotic fluid, with peak levels of EP15 seen at 10–15 weeks and peak levels of EP14 at 20–24 weeks. Since these proteins were undetectable in peripheral sera by this method it is suggested that their major route of secretion during pregnancy is into the uterine lumen and not into the vascular system.

Screening for intrauterine growth retardation by umbilical artery velocity waveform analysis by E. Hockney & A T. Letchworth. Royal Hampshire County Hospital

A study in the antenatal clinics of a district general hospital assessed umbilical artery waveform analysis as a screening test for the small-for-gestation fetus. The equipment used was a continuous-wave Doppler device operating at a transient receive frequency of 4 MHz and an Angioscan spectrum analyser The within and between observed variation for systolic/diastolic ratio was 11% and 11·4%, respectively Patients were assessed at 30 weeks gestation by umbilical artery waveform analysis, assay of human placental lactogen (hPL) and fundal height measurement. A systolic/diastolic ratio above the 90th centile, hPL level below 3·5 mg/l, and a fundal height below the 10th centile were considered as abnormal. The sensitivity and predictive value of a positive test in predicting a birthweight below the 10th centile for gestation was assessed in 273 consecutive patients. In the 23 pregnancies with small-for-dates infants (prevalence = 8·4%) umbilical artery waveform analysis had a sensitivity of 30% compared with 13% for hPL levels. It was impossible to calculate the sensitivity of fundal height measurements as none of the small-for-dates babies was detected. The predictive value of 50% for hPL levels was superior to that of 26% for the umbilical artery waveform. It would seem that the umbilical artery waveform is potentially a useful predictive test for the small-for-gestation fetus that can be used in an antenatal clinic and larger studies are indicated.

Fat cell size and lipolysis: a serial study of artificial feeding and breast-feeding women by M. A. Radcliffe†, D. M. Campbell*† & A. D. Smith†. Departments of *Obstetrics and Gynaecology and †Physiology, University of Aberdeen

Previous studies of fat cell size and lipolysis in women postnatally have not taken account of lactational status. We have measured fat cell size and both basal and catecholamine-stimulated lipolysis in subcutaneous fat tissue aspirated from the buttock serially at 38 weeks gestation (visit 1), 3–6 days postpartum (visit 2), and 5–6 weeks postpartum (visit 3) in normal subjects of whom six fed their infants artificially (Group A) and nine from the breast (Group B). None received oral contraceptives. Body weight and serum hPL, 17β-oestradiol, progesterone, prolactin (PRL) and insulin levels were also measured. Mean body weight was similar in each group and there were no differences in weight changes during the period studied. Serum hormone levels followed established patterns: mean serum PRL was significantly greater in Group B than in Group A at visit 3 ($P<0·05$). Mean fat cell diameter was less in Group B (98·0 SD 10·1) than in Group A (112·0, SD 5·0) at visit 1 ($P<0·01$), otherwise there were no significant inter-group differences. Mean fat cell size decreased progressively in Group A, but paradoxically increased in Group B between visits 1 and 2 ($P<0·02$) before falling to a level not significantly different from that in Group A at visit 3. The mean rates of basal and of 10-5M isoprenaline-stimulated lipolysis did not differ between the groups at any visit and there were no clear inter-visit differences in lipolytic rate. Although the pattern of change in fat cell size was different between the two groups, we have found no explanation for this. The inter-group findings suggested that clear differences do not arise in body weight, or lipolysis between lactating and non-lactating women during the first 5–6 weeks postpartum.

Effect of race on maternal symphysis to fundal height, and weight by I. Stabile & J. G. Grudzinskas. Academic Unit of Obstetrics and Gynaecology, The London Hospital Medical College

A prospective study of the clinical value of symphysis to fundal height measurements was based on the entire antenatal population attending one consultant clinic at The London Hospital. The racial mix included 45·1% Bangladeshis, 40·6% white Europeans and 14·3% from other countries of origin. The reproducibility of the method was investigated in a group of six patients measured six times by five different observers. The intra-observer variation ranged from 1·3 to 5·6%, while the inter-observer variation was 4·8%. A total of 523 observations on 84 Bangladeshi women, and 270 observations on 57 European women were used to construct centile charts for symphysis to fundal height from 16 to 40 weeks of amenorrhoea. The differences between the two population groups were greater after 32 weeks gestation, when the 10th centile for the European women approached the median for the Bangladeshi women. On average the Bangladeshi women were 8 cm shorter and 11·5 kg lighter than the European women at booking. In a small group of women who booked between 16 and 20 weeks and were delivered at term, the mean weight gain was 8·6 kg (SD 3·75) for 20 Bangladeshi women, and 9·6 kg (SD 3·94) in 24 European women. This difference was not statistically significant. There was a significant difference, however, in the proportion of women who actually lost weight in the third trimester (Bangladeshi, 10·7%; European, 3·4%).

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CORRESPONDENCE

Betamimetic drugs in the prophylaxis of preterm labour: extent and rationale of their use

Dear Sir,

Dr Keirse [*Br J Obstet Gynaecol,* (1984) **91,** 431-437] has presented the results of a questionnaire about the prophylactic use of tocolytics and has reminded us that there is no evidence of their effectiveness. We have relevant data from the Oxford Obstetric Data System about asthmatic patients who were delivered in the John Radcliffe Hospital in Oxford. From 1981 to 1984, 838 asthmatic patients were delivered; of these, 201 were routinely taking betamimetics while 637 were not. Betamimetic administration was not associated with length of gestation (Table 1). There was no difference between the two groups, in the rate of either preterm delivery or postmaturity. These figures would be misleading if the rates of induction or elective caesarean before labour were different in the two groups, but this was not the case.

This is only indirect evidence of the lack of effectiveness of oral prophylactic betamimetics for preventing preterm labour. Nevertheless it contrasts with the same type of analysis performed by Lewis & Schulman (1973), of 103 patients taking aspirin during pregnancy, for rheumatic disease. These women showed a highly significant increase in the length of gestation and in postmaturity when compared with untreated rheumatic patients.

A real effect of betamimetic drugs could be masked if the women taking the drug were at greater risk of preterm labour than the other asthmatics. This seems unlikely for two reasons. First, the proportion of patients who had experienced a previous preterm delivery was similar in both groups and this is recognized as the single most predictive risk factor. Second, there is no evidence that severe asthma increases the risk of preterm delivery and though there were more antenatal admissions in the betamimetic group, the excess was mainly due to maternal medical complications without fetal involvement.

Finally the dose of drug might cause the lack of difference between the two groups, if a minimum blood concentration were necessary for prophylactic betamimetics to be effective. This would not be in agreement with studies on salbutamol by Neville *et al.* (1977) which showed no difference in metabolic effect between aerosol and intravenous administration.

The rationale for prophylactic use of betamimetics does not seem to lie either in the results of controlled trials, or in the observation

Table 1. Length of gestation and antenatal complications in 838 asthmatic women 1981–1984

	Taking betamimetics	Not taking betamimetics	Relative risk*	Significance of differences between groups
Total no	201	637		
Gestation at delivery (weeks)				
<37	10	34	0·93	n.s.
37–40	141	461	0·97	n s
>40	50	142	1·12	n.s.
Induced labour or elective section, before labour	67	209	1·02	n.s.
History of preterm delivery	6	22	0·86	n.s.
Antenatal admission	66	155	1·34	<0·05

*Relative risk figure shows the risk of each factor in the group taking betamimetics compared to the group not taking betamimetics.

of a decrease in preterm births associated with their use or even as is the case with drugs like aspirin from extrapolating their effect in other indications.

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Quickening—a re-evaluation

Dear Sir,

The challenging of classical notions and common practices is a sound exercise and we wish to compliment Drs O'Dowd and O'Dowd for having reassessed the clinical value of using the data of quickening for estimating duration of gestation [*Br J Obstet Gynaecol* (1985) **92**, 1037–1039]. The authors may be interested to learn that having conducted a comparable study 6 years ago we discontinued this time-honoured practice in the light of the extremely wide ranges of last menstrual period-to-quickening intervals found in 242 pregnant women (138 nulliparae) with known gestational ages (De Gezelle *et al.* 1979).

Fetal movements were first noted by the nulliparae at a mean duration of gestation of 138 (SD 12; range 104–170) days and by the parous women at 128 (SD 12; range 95–178) days and the difference between them was highly significant. We also found that in nulliparae, the sex of the unborn had no effect on the time of onset of maternal perception of fetal activity. However, parous women bearing a female fetus felt quickening significantly ($P<0\cdot01$) earlier, which is in conflict with the ancient belief that earlier quickening is indicative of a male baby. Linear regression analysis of maternal age in relation to quickening showed no correlation. For nulliparae we found only a borderline correlation ($P = 0\cdot05$) between the time of quickening and the infant's weight at birth, i e. a shorter mean interval between the last menstrual period and quickening for heavier babies.

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BOOK REVIEWS

Preterm Labour and its Consequences (Proceedings of the Thirteenth Study Group of the Royal College of Obstetricians and Gynaecologists (February 1985)) edited by R. W. Beard & F. Sharp. Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG. 402 pages with figures and tables, £15.00 (plus postage)

This is the first time that the RCOG study group system has re-examined an important topic. The 'silver book' on preterm labour was published in 1977. Since then the streamlined editorial process has resulted in the interval between the conference in February 1985 and the publication in June of the same year being very commendably even shorter.

During these eight years, a revolution has occurred in perinatal care. Most of the improvement in the healthy survival of preterm infants has been achieved by intensive neonatal care. This, in turn, has given obstetricians opportunities to deliver, with much less trepidation than before, very small babies. Provided such babies are delivered gently, are in good condition at birth and are born where expert intensive care can start at once, even those weighing no more than 750 g stand a better than even chance.

The membership of the study group was chosen with great judgement and the contributors have either summarized their own and others' very recent work or are actually reporting new work. The influence of the National Perinatal Epidemiology Unit (NEPU) pervades the proceedings. For example, during discussions, every aspect of management is judged by whether it has been, or should be, the subject of a prospective randomized controlled (preferably blind) trial. The NEPU itself, in one paper, brings together the results worldwide of all prospective controlled trials involving the use of tocolytics in preterm labour. This paper demonstrates how difficult it must be to measure the 'end-points' of such treatment; but the conclusions are not as nihilistic as might be anticipated.

There are contributions on epidemiology, on risk factors both for preterm births and for the infants when born; on recent work on the onset of labour (though no-one really yet knows why the timing goes wrong); several on fetal physiology—endocrine, neurological and cardio-respiratory; the role of infection both in the onset of labour and in the pathology of mother and baby; on whether and when vaginal or abdominal delivery are preferable; on the management of the preterm neonate; and on the audit of perinatal management. This list is not exhaustive, and it would be wrong to omit mention of the French Haguenau perinatal study and of a fascinating report on the influence of psychological stress in low birthweight and in preterm labour.

The principal omission, which was obviously intentional, is the role of multiple pregnancy in preterm labour. That apart, anyone practising obstetrics or neonatal paediatrics and wishing to read an update on the current state of knowledge must hurry and buy this book. It is more expensive than its predecessor, but it is even better value for money.

K. John Dennis

The Role of Prostaglandins in Labour (No. 92 The Royal Society of Medicine Services Limited International Congress and Symposium Series) edited by Clive Wood. Royal Society of Medicine Series Limited, 1 Wimpole Street, London W1M 8AE, 100 pages with figures and tables, £10.00

This volume contains a series of papers presented at a symposium held in April 1985 on the role of prostaglandins in labour. It is divided into two parts: examination of the role of endogenous prostaglandins in labour and the role of exogenous prostaglandins in the induction of labour. Contributions are principally from well known authors in the field. The first part of the book explores control of prostaglandin production in both man and animals. There is a useful description of current work on the regulation of prostaglandin biosynthesis in uterine and placental tissues and fetal membranes. An interesting photograph shows the immunohistochemical localization of the site of prostaglandin synthesis in human myometrium in late pregnancy. Two chapters are devoted to studies concerning the interaction between oxytocin and prostaglandins in labour. The section on induction of labour has a useful review of the development of the use of prostaglandins in this field. Subsequently studies using prostaglandins in women with either high or low Bishop scores are described. Preliminary data on the European Multicentre trial of intracervical PGE_2 in triacetin gel are presented. In addition prostaglandin release using various vaginal delivery systems (tablet, pessary, gel) is explored.

To summarize, this short book provides an excellent up-to-date review on prostaglandins and labour, and the speed in publication (a few months) is to be commended. Despite the rapidity in production there are no glaring editorial errors. The only criticism that one might make is that detailed prior knowledge of prostaglandin metabolism would be helpful before reading the first section. However, this point does not detract that this short book provides a useful way by which obstetricians can keep up with the current literature on the subject.

Margaret C. P. Rees

Ultrasound in Perinatal Care Volume 1 in the series 'Perinatal Practice' edited by M. J. Bennett. John Wiley and Sons, Chichester, 1984, 187 pages with figures and tables, £19.50

This is apparently the first in a proposed series of five volumes which aim to bridge the gap between ultrasound in obstetrics and its rapidly expanding use in neonatal medicine.

This first volume contains ten chapters by twelve contributors half of whom come from the United Kingdom.

In common with most books on diagnostic ultrasound these days it contains an initial chapter covering the technical aspects of ultrasound equipment usage. Although the contents of this chapter has been well covered elsewhere this particular contribution is readable and readily understandable and will be helpful to those approaching the subject for the first time.

There follows a discussion on the reproducibility of ultrasound measurements. This chapter includes discussion of many of the more extravagant claims which have been published in recent years for the prediction of fetal birthweight, but the papers are not critically discussed and I suspect the detailed statistical analyses will be beyond the comprehension of many clinical readers. The role of ultrasound in obtaining measurements of many other parts of the fetal anatomy is discussed by reference solely to the author's personal results and much of the main body of world literature on the subject has not been quoted or referenced.

Probably the best section in the book is that covering amniocentesis and fetoscopy. Only a short time ago these were procedures carried out only in specialist centres and this book reflects their widening availability in other centres.

Conversely the weakest section of the book is undoubtedly that on neonatal intraventricular haemorrhage. The images illustrating this section are technically poor and were obtained with inappropriate apparatus. Once again the author of this section relies too heavily on his own experience and refers little to the wealth of information from other authors.

A significant omission from this book is the role of ultrasound in imaging the abdominal organs of the neonate, particularly liver and kidneys. This seems somewhat surprising since there is an excellent section on paediatric echocardiography.

The introduction of this new series is timely since the specialty of perinatal imaging is new and rapidly growing. Unfortunately this book has many omissions and some of its contributions are less than accurate. Despite this it may serve as a useful introduction to the subject for those who have little or no personal experience.

H. B. Meire

In Vitro Fertilisation and Donor Insemination. Proceedings of the Twelfth Study Group of the Royal College of Obstetricians and Gynaecologists, November 1984, edited by W. Thompson, D. N. Joyce & J. R. Newton. 402 pages with figures and tables, £12.00

This volume published by the Royal College of Obstetricians and Gynaecologists is a compendium of the papers delivered at the meeting of the Study Group on 'In Vitro Fertilisation and Artificial Insemination by Donor' in November 1984. This is writing at the advancing front of knowledge and much of it will date rapidly. It is nevertheless a landmark: a definitive statement of what we knew at the end of 1984 and a manual of practice for years to come.

There is a neat balance between practicality (*vide* Templeton on ovulation timing or Craft on oocyte recovery) and philosophy as exemplified by Ann McLaren's essay on the control of implantation. The book is dominated but not swamped by in-vitro fertilization. There is, for instance, a guide to the management of an AID clinic by Stewart which may be useful to the licensing authority which is to be established under Warnock. I liked particularly its stress on the confidentiality of AID records and agree that NHS case sheets are not the proper place for this information. Newton gives an authoritative account of the present organization of AID in Britain. It is to be hoped that annual returns to the College will be made a condition of the granting of an AID licence.

There are few university departments of obstetrics and gynaecology in the country which do not provide an in-vitro fertilization service and none which do not aspire to do so. For them this book is a *sine qua non*, and the same applies in hardly less measure to all those involved in the provision of AID services. The tremendous advance in the understanding of reproduction and in the treatment of infertility had its genesis here but as with many other scientific discoveries the harvest is being gathered in elsewhere. It is to our shame and eternal loss that the government has given so little backing to IVF that its development has depended almost entirely upon commercial exploitation and charity. It speaks volumes for the talent and devotion of our clinicians and scientists that, under these circumstances, they can still make a contribution of the kind contained in this book. It well deserves the awful permanence of print.

As might be expected from writings which were not refereed the individual contributions vary greatly in intent, style and length. On the one hand there are a number of good short reviews. The work by Hull on monitoring the ovarian cycle is a fine example of review writing at its best. From the immense array of published material at his disposal he has winnowed the critical facts and marshalled them in a closely argued account. In 13 pages of text he has packed all that the practitioner or the MRCOG candidate needs to know at this time. He was much helped by the numerical superscript technique of citing references which enabled him to put in 44 references without making the text unreadable. On the other hand, some contributors have adopted the format and content of an original article in a scientific journal. The work by Lenton *et al.* on the endocrine effects of aspirating the follicle would be readily accepted by the most prestigious journals in the field.

There are printed discussions, not very carefully edited by the speakers, after each presentation. *Quot homines tot sententiae.* For my part they did nothing to illuminate the text which in any case did not require it. Discussions are proper to a meeting, not a book. I hope the College will drop them from future reports of the activities of its Study Groups.

Arnold Klopper

Books received some of which may be reviewed at a later date

Respiratory Control and Lung Development in the Fetus and Newborn. The Scientific Basis of Clinical Practice (Reproductive and Perinatal Medicine (111)) edited by B. M. Johnston & P. D. Gluckman. Perinatology Press, Ithaca, New York, 1986, 427 pages with figures and tables, $50

Blood Disorders in Pregnancy edited by Russell K. Laros, Jr. Lee & Febiger, Philadelphia, 1986, UK agents are Quest-Meridien Ltd, Beckenham, Kent, 245 pages with figures and tables, $35.75

Infection in the Female second edition by William J. Ledger. Lee & Febiger, Philadelphia, 1986, 293 pages with figures and tables, $42.25

Manual of Clinical Problems in Obstetrics and Gynaecology (with annotated key references) second edition edited, by Michel E. Rivlin, John C. Morrison & G. William Bates. Little Brown & Co., Boston/Toronto, 1986, 449 pages, $10.95

Birth Matters Issues and Alternatives in Childbirth edited by Ros Claxton. Unwin Paperbacks, London, 1986, 253 pages, £3.95

Pregnancy and Childbirth by Sheila Kitzinger. Penguin Books Ltd., London, 1986, 351 pages, £5.95

Birthwise. Having a Baby in the 80's by Peter Saunders. Sidgwick & Jackson, London, 1986, 216 pages, £4.95

The Dilemma of Abortion by Edwin Kenyon. Faber and Faber Ltd., London, 1986, 283 pages, £6.50

Essentials of Obstetrics and Gynaecology third edition by James Willocks, Churchill Livingstone, Edinburgh, 1986, 277 pages, £7.95

Recent Advances in Sexually Transmitted Diseases 3 edited by J. D. Oriel & J W. R. Harris. Churchill Livingstone, Edinburgh, 1986, 277 pages with figures and tables, £35.00

The Climacteric in Perspective edited by M. Notelovitz & P. van Keep. MTP Press, Lancaster, 1986, 463 pages with figures and tables, £45.00

Prostaglandins and their Inhibitors in Clinical Obstetrics and Gynaecology edited by M. Bygdeman, G. S. Berger & L. G. Keith. MTP Press, Lancaster, 1986, 430 pages with figures and tables, £95.00

Having a Baby in Europe Report on a Study (Public Health in Europe No. 26) World Health Organization Office for Europe, Copenhagen 1986, 157 pages, Sw Fr 13

4th edition

Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates

Edited by **C. R. Whitfield,** MD, MB BCh, FRCP, FRCOG, Regius Professor of Midwifery, University of Glasgow and Honorary Consultant Obstetrician and Gynaecologist, Queen Mother's Hospital and Western Infirmary, Glasgow
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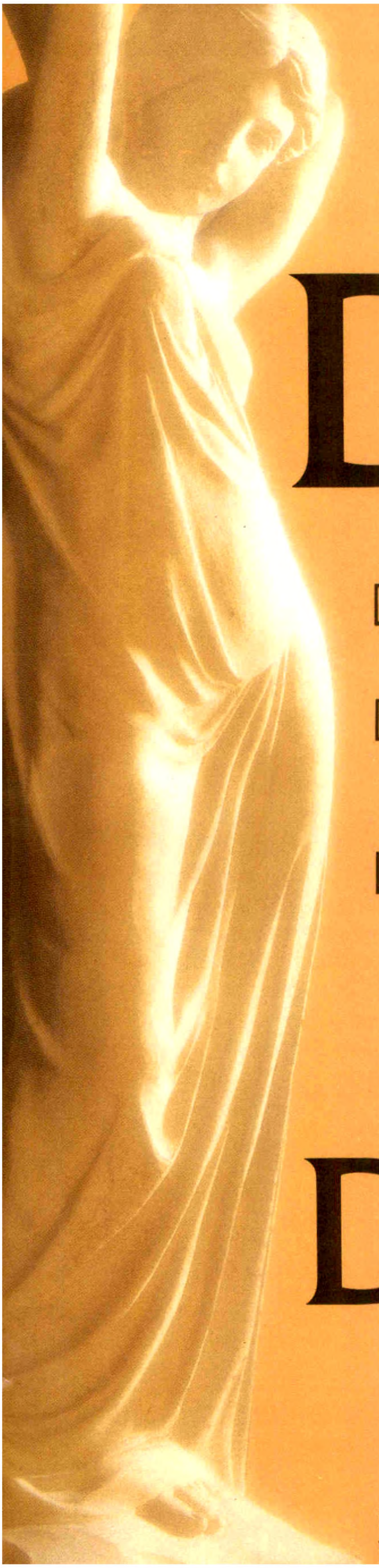

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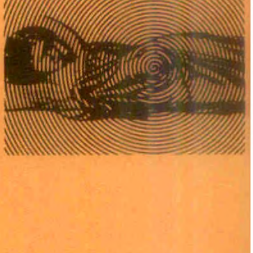

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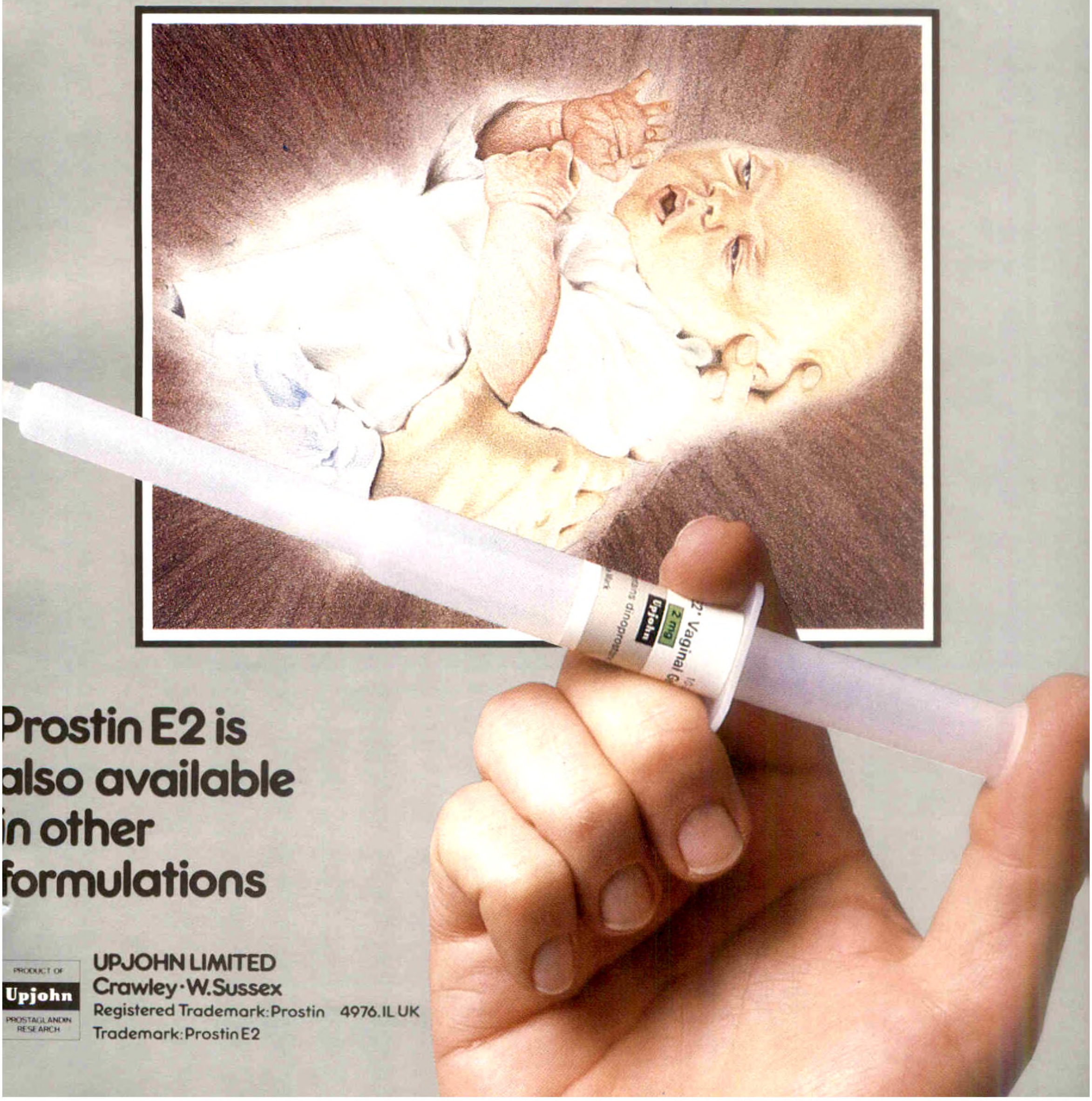

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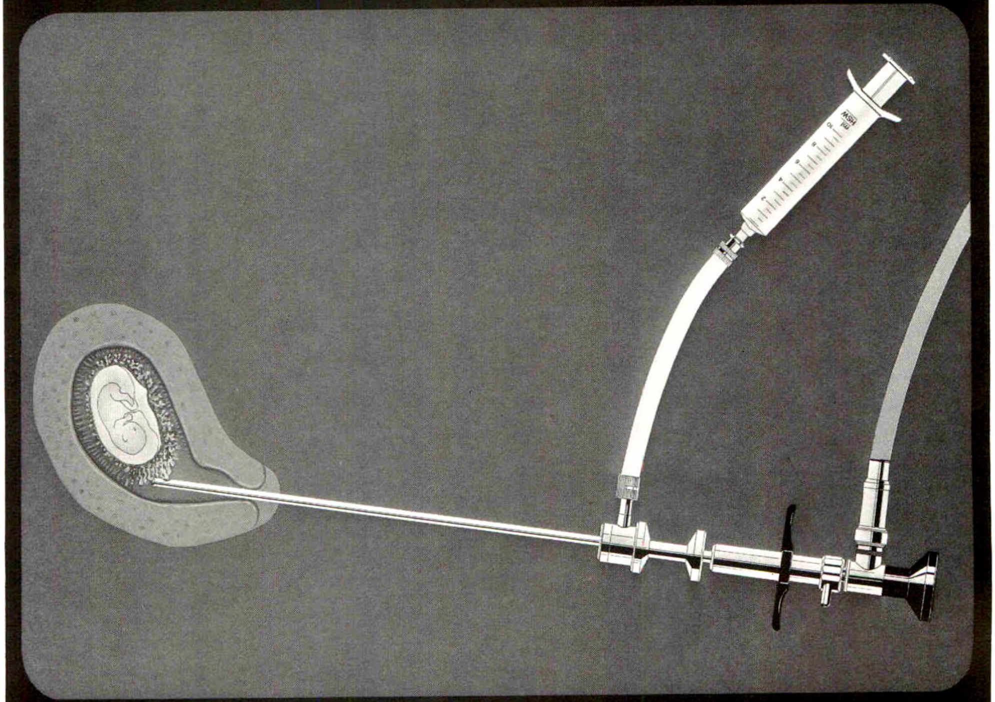

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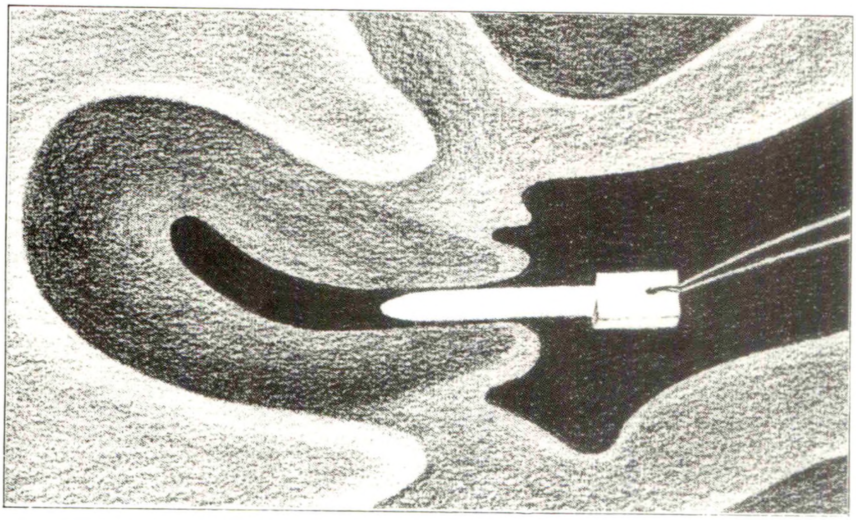

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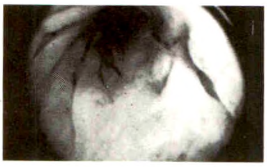

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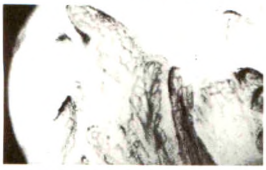

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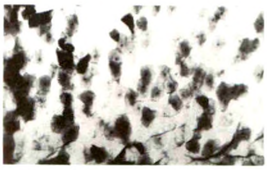

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British Journal of Obstetrics and Gynaecology
September 1986, Vol. 93, pp. 897

COMMENTARY

Genetics of hypertension in pregnancy

It is not often that one has the privilege to read and witness a study as unique as Leon Chesley's investigation (this issue p. 898) into the family history of women with eclampsia. Here it is, a model to all investigators, young and old, into the single-minded pursuit of excellence and persistence in trying to answer a single question. Does pre-eclampsia have a genetic basis? To answer this question, Chesley identified a cohort of eclamptic women delivered in the Margaret Hague Maternity Hospital between 1931 and 1951 and then personally pursued the obstetric history of the daughters, grand-daughters and daughters-in-law by obtaining their obstetric records from more than 150 hospitals. Desmond Cooper has analysed the data and the authors have concluded that the disorder is highly heritable, and is consistent with a single gene model. There are, as the authors freely admit, difficulties inherent in the information available from the case records, and the problems of making the diagnosis of pre-eclampsia as distinct from eclampsia. The concept is not new, but the distinction between genetic and environmental factors has always been difficult. The inclusion of daughters-in-law to provide a suitable control group makes provision for possible environmental effects.

The study is a logical conclusion to the work of Chesley *et al.* (1961) and Adams & Finlayson (1961) who demonstrated an increase in the incidence of pre-eclampsia in the sisters of pre-eclamptic women. Cooper & Lister (1979) suggested that a single recessive gene could determine susceptibility to pre-eclampsia, and all the evidence points to the likelihood of a single gene hypothesis in its aetiology.

So what are the implications of such a finding? It is clear that there are many factors that influence the development of pre-eclampsia such as twin pregnancies, diabetes, molar pregnancies and severe rhesus isoimmunization which increase the incidence of pre-eclampsia and act against the concept of a single gene inheritance. Furthermore, there have been numerous publications over the years that suggest climatic and environmental factors affect the incidence of pre-eclampsia and eclampsia, and these cannot be lightly discarded. It seems likely that any single recessive gene must act by some specific enzyme induced activity, that is, at least in part, activated by one or several substrate-led deficiencies.

The particular importance of all these observations is that it points to the possibility of being able to identify an 'at risk' population. It must be remembered that pre-eclampsia most commonly occurs in primigravidae and is not generally a recurrent condition, and any hypothesis that attempts to explain the nature and occurrence of pre-eclampsia must take that into account. Furthermore, it is important to realize that the present hypothesis is limited to an analysis of maternal factors and takes no account of either paternal or fetal genetic constitution.

Not one of these considerations detracts in any way from this superb study of the family histories of women with eclampsia. It is unlikely to be repeated unless some specific and easily identified marker is described that will enable us in the future to perform long-term studies of genetic and clinical data in women who develop severe hypertension and proteinuria in pregnancy.

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Department of Obstetrics & Gynaecology
University Hospital
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British Journal of Obstetrics and Gynaecology
September 1986, Vol. 93, pp. 898–908

Genetics of hypertension in pregnancy: possible single gene control of pre-eclampsia and eclampsia in the descendants of eclamptic women

LEON C. CHESLEY, DESMOND W. COOPER

Summary. Our report concerns the incidences of pre-eclampsia and eclampsia in 147 sisters, 248 daughters, 74 granddaughters, and 131 daughters-in-law of women who have had eclampsia. The disorder is highly heritable. We have analysed the data in two ways, firstly, as a single gene condition and, secondly, as a multifactorial condition. The observed incidences fit closely with the single gene model with frequency of the putative gene being 0·25. When Falconer's method of estimating heritabilities of discrete characters is used, estimates of 120% (sisters), 88% (daughters), and 105% (granddaughters)—none significantly different from 100%—are obtained. Insofar as possible, our definition of pre-eclampsia corresponds with EPH in the descriptive classification of the Organisation Gestosis and to 'severe pre-eclampsia' in Nelson's classification. The women were delivered in many different hospitals, however, and many records fail to provide all of the essential information

Several bodies of evidence indicate that pre-eclampsia and eclampsia are largely under genetic control. The early obstetric literature has many reports of eclampsia in sisters, mothers and daughters—usually one daughter, but up to four (Elliot 1873) or five (Berg 1934). Hinselmann (1924), in his review of the literature, agreed with Scanzoni (1867) that eclampsia was then so common that the familial cases might be mere coincidence. The first systematic prospective study of the familial factor was made by Chesley *et al.* (1961). They reported the incidences of pre-eclampsia and eclampsia in the first pregnancies of sisters and daughters of eclamptic probands to be greatly increased over the incidence in the population of the maternity hospital. (Because many studies have established that pre-eclampsia and eclampsia are predominantly disorders of first pregnancies, all studies referred to in our paper are based upon data from first pregnancies, unless we state otherwise.)

Using data from Aberdeen, Adams & Finlayson (1961) compared the incidences of pre-eclampsia in the sisters of pre-eclamptic probands and those of women having had normotensive pregnancies, and found a similar increase. Chesley *et al.* (1968) extended their series of daughters and sisters and added daughters-in-law as controls. They confirmed that the blood relatives had a much higher incidence and that the incidence in the daughters-in-law was that of the population. Cooper & Liston (1979)

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DESMOND W. COOPER *Professor of Biology*

Correspondence. Leon C. Chesley, PhD, Box 24, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203, USA.

analysed the data of Chesley *et al.* (1968), Adams & Finlayson (1961), and further data from Aberdeen. They put forward the hypothesis that a single recessive gene determines the susceptibility to pre-eclampsia, but could not decide whether the gene acted in the mother or in her fetus. Again using data from Aberdeen, Sutherland *et al.* (1981) studied the incidences of pre-eclampsia in the first pregnancies of mothers and mothers-in-law of affected probands and of mothers and mothers-in-law of an unaffected control group; from their findings, they concluded that the maternal genotype alone was responsible and that the incidences were compatible with the single gene hypothesis, although polygenic inheritance could not be excluded.

Two other studies should be mentioned, although they were not confined to first pregnancies. Brocklehurst & Ross (1960) reported 11 cases of eclampsia in eight women and 'many cases' of pre-eclampsia in other women of four generations of a closely inbred family. Humphries (1960) selected 100 women with 'hypertensive toxemia of pregnancy' (probands) and 200 others having had normal pregnancies, all of whom had been born in the Johns Hopkins Hospital, in Baltimore, Maryland. Analysis of their mothers' obstetric charts for the pregnancies of which the patients were born showed that 28% of the mothers of the probands had had hypertension as against 13% of the mothers of the controls. However, 23% of the probands were multiparae and were not likely to have had pre-eclampsia. Furthermore, only a minority of the mothers had been primigravidae at the time and only 40% of the maternal hypertensive pregnancies had occurred in primigravidae. It seems probable that most of the maternal hypertensive 'toxemias' had not been pre-eclampsia, particularly since follow-up study of the mothers 10 and 20 years after the index pregnancies revealed that hypertension was more prevalent among the mothers of the probands than among the mothers of the control group.

The purpose of our paper is to give a complete summary and analysis of data collected by the senior author over the 49-year-period from 1935 to 1984. We show that this body of data gives a good fit with the predictions of the hypothesis that pre-eclampsia is determined by a single recessive gene acting in the affected women rather than their fetuses.

Subjects and methods

Our primary source of information has been the women who had eclampsia between 1931 and 1951 in the Margaret Hague Maternity Hospital, Jersey City, New Jersey and whom we have re-examined at intervals since 1935. All information given to us by the women has been verified, supplemented or modified by marriage and birth registrations in the state registry of vital statistics in Trenton, New Jersey and in other states as needed. Moreover, the registries have enabled us to 'reconstruct' and trace the descendants of the women dying of eclampsia or soon after. As an example, one woman died of eclampsia in 1932, leaving 9 children; we have traced all 84 of her descendants, living in seven states, as confirmed by correspondence with several of them.

In the analysis of the pregnancies of daughters, granddaughters and daughters-in-law we have seen obstetric charts from more than 150 hospitals. In some instances the only positive information to be gleaned is that the woman probably had a baby.

Data on 75 daughters-in-law, all the sisters delivered in the Margaret Hague Hospital, and 187 daughters were given in Chesley *et al.* (1968). A further 56 daughters-in-law, 61 daughters and all granddaughters are reported on for the first time here. Information on daughters in Chesley *et al.* (1968) was almost complete; 348/363 (96%) of all daughters who were 15 or older at that time had been traced. The proportion of daughters and granddaughters traced in the period 1969–1984 cannot be given because nearly 100 of the original mothers have now died, and contact with many of the families lost.

Definition of pre-eclampsia

Chesley *et al.* (1968) used the word 'toxemia' for what we now call pre-eclampsia. 'Toxemia' is an ambiguous misnomer, used by some as synonymous with pre-eclampsia and by others as a broader term including various hypertensive disorders complicating pregnancy. What we here call 'pre-eclampsia' is roughly equivalent to 'severe pre-eclampsia' in Nelson's (1955) classification, with the exception that not all women had proteinuria (but usually had later normotensive pregnancies). As noted in the text, information about oedema and proteinuria often was not available, but insofar as possible what we call pre-eclampsia is equivalent to EPH in the

Table 1. Observations recorded in hospital charts of primigravid daughters of eclamptic women

	Blood pressure					
	All readings hypertensive					
	Single recording	Two or more	Normal and hypertensive readings	No recording	One or more all normal	Totals
Cases	4	61	45	25	113	248
Proteinuria						
Negative or trace	1	10	20	2	46	79
One plus or more	2	35	12	1	8	58
No note about urine	1	16	13	22	59	111 (44·7%)
Oedema						
None or slight	2	9	17	0	41	69
Present	0	35	7	3	9	54
No note about oedema	2	17	21	22	63	125 (50·4%)
Proteinuria and oedema						
Neither	1	3	12	0	34	50
Both	0	22	3	1	0	26
One not noted	2	32	22	4	27	87 (35·1%)
Neither noted	1	4	8	20	52	85 (34·3%)
Diagnosis						
Borderline	1	1	12	0	0	14
Pre-eclampsia	0	60	2	3*	0	65

*See text.

descriptive classification used by the Organisation Gestosis (Rippmann 1970).

Results

Pregnancies in daughters

The diagnosis of pre-eclampsia or eclampsia was made in the first viable pregnancies of 65 of the 248 daughters, or 26·2%. First pregnancies are said to have aborted in 15, or 6%, but they probably were underreported. The analyses pertain to the first pregnancies carried to viability and include two with pre-eclampsia known to have followed abortions. Seven first pregnancies were complicated by placental abruption, three in association with pre-eclampsia. Eight first pregnancies resulted in stillbirths (32·3 per 1000), four in association with pre-eclampsia; there were at least two neonatal deaths, but the total is uncertain; one of the two was associated with maternal pre-eclampsia.

The recordings in the hospital charts are summarized in Table 1. There was no recording of blood pressure in 25 primigravidae (10·1%) and among the 25 there was no analysis of urine or note as to the presence or absence of oedema in 20 (8·2% of all cases). Three of the women in that group have been regarded as having had pre-eclampsia, one on the basis of her private physician's letter and two because they said that they had been admitted to the hospital several days before labour because of high blood pressure and swelling, none of which was recorded in their charts although they had been in the hospital for some time before the onset of labour; one of them had a stillbirth.

Sixty of the women regarded as having had pre-eclampsia had sustained hypertension with no recordings of a normal pressure at the time; the remaining two had an interspersion of hypertensive and normotensive readings and both had proteinuria and oedema. Fourteen women were classified as borderline; some may have had pre-eclampsia but there was not enough information to sustain the diagnosis.

Overall, there was no recording of urine analysis in 44·7%, although it is half a millenium since Savonarola wrote that the urine of a pregnant woman should be regarded with solemnity. The charts contained no note as to the presence or absence of oedema in 50·4% of the cases, and information about both urine and oedema was absent in 34·3%; one or the other was missing in another 35·1%.

Table 2. Viable pregnancies in daughters of eclamptic women

		Hypertensive									
		Recurrent		New†		Eclamptic		Placental abruption		Stillbirth	
Pregnancy	Cases	No	%	No.	%	No	%	No.	%	No	%
First	248	0	0	60	24·2	5	2·0	7(3)*	2·8	8(4)*	3·2
Second	161	6	3·7	4	2·5	1	0·6	4(3)*	1·8	3(2)*	1·8
Third	101	1	1·0	3	3·0	1	1·0	2(0)*	2·0	1(1)*	1·0
Fourth	33	1	3·0	0	0	0	0	1(1)*	3·0	1(1)*	3·0
Fifth through sixteenth	28	0	0	1	3·6	0	0	0	0	0	0
Totals	571	8	1·4	8	1·4	7	1·2	14(7)*	2·5	13(8)*	2·3

*Associated with hypertensive pregnancies.
†Hypertension in second or later pregnancy following normotension in first

Table 3. First viable pregnancies of daughters of eclamptic women

		Pre-eclamptic		
Daughters	Total cases	No	%	Heterogeneity χ^2
(a) Born of eclamptic pregnancy	84	26	30·9	
versus				1·48
Born of another pregnancy	164	39	23·8	(1 d.f.)
(b) Born of mothers' first pregnancies	159	39	24·5	
versus				1·71
Born of later pregnancies	89	26	29·2	(1 d.f.)
(c) Mother hypertensive in long-term follow-up	121	35	28·9	
versus				0·90
Mother normotensive in long-term follow-up	127	30	23·6	(1 d.f.)
(d) Birth orders				
1	88	21	23·9	
2	65	17	16·2	3·63
3	45	9	20·0	(3 d.f.)
4 or later	50	18	36·0	

None of the χ^2 is significant at the 5% level
d.f., Degrees of freedom.

Table 4. Familial incidence of pre-eclampsia/eclampsia in first viable pregnancies of daughters of eclamptic women

				Pre-eclampsia	
Daughters per family	Families	Daughters	No with pre-eclampsia/eclampsia	% by daughters	% by families
1	93	93	23	24·7	24·7
2	42	84	18	21·5	35·8
3	15	45	10	22·2	46·7
4 and 5	4 + 2	16 + 10	12 + 2	53·9	66·7
Totals	156	248	65	26·2	32·0

Among the 65 daughters thought to have had pre-eclampsia, only 38 are known to have had proteinuria of at least one plus. The urines of 10 were negative for protein or had only a trace, but in most instances only one test had been done, often several days after delivery. The urines of the remaining 17 had not been tested. Thus, the diagnosis of pre-eclampsia must be suspect in 27 of the 65 cases. Although proteinuria is a hallmark of pre-eclampsia and eclampsia, it usually is of late onset and sometimes absent. Sibai *et al.* (1981) noted that 14 (21%) of 67 eclamptic women had had the onset of convulsions before or without the appearance of proteinuria. Moreover, the proteinuria is transient and usually disappears shortly after delivery.

All ten of the women without significant proteinuria have had later pregnancies, which were normotensive in eight; the other two had recurrent hypertension. Fourteen of the 17 whose urines had not been tested have had later pregnancies, all of which were normotensive. Normotensive pregnancies following hypertension in the first support the diagnosis of pre-eclampsia in the first. Overall, 54 of the 65 have had later pregnancies carried to viability, 47 (87%) with all pregnancies normotensive. Seven women had hypertension in eight later pregnancies.

The diagnoses of pre-eclampsia made in the hospital where the women were delivered have been rejected in two cases because of the lack of recorded findings in one; the other had hypertension before pregnancy, in four pregnancies, and at follow-up, and a diagnosis of 'Goldblatt kidney' has been made. More commonly, we have diagnosed pre-eclampsia in women whose hospital charts do not bear that diagnosis, especially in private patients. An extreme example is a 15-year-old girl whose mother had had eclampsia at age 15; the patient's chart shows an acute onset of hypertension, heavy proteinuria, and oedema, and that she was sent home. A few days later she was admitted with convulsions (nine), in coma, and was on the 'Danger List' for 24 h. All signs abated rapidly after delivery. The final diagnoses in the chart were 'Normal Pregnancy, Normal Delivery, Normal Puerperium'.

Table 2 summarizes the first and later pregnancies of the 248 daughters of eclamptic women, up to 1978 when the collection of data was ended. Seven daughters, or 1 in 35, have had eclampsia, five in first pregnancies. One woman had normal first and third pregnancies with eclampsia in the second. The other had normal first and second pregnancies followed by eclampsia in the third. In all, eight women had newly hypertensive pregnancies following normotensive first gestations. One had eight normotensive pregnancies, probable pre-eclampsia (acute hypertension and proteinuria) in the ninth, followed by three normotensive pregnancies.

Table 3 indicates that the incidence of pre-eclampsia in the daughters of eclamptic women is not affected by whether or not they were born of the eclamptic pregnancies, whether they were born of the mothers' first or later pregnancy, whether or not the mothers eventually developed chronic hypertension, or by the daughters' birth orders. The familial incidence of pre-eclampsia is independent of the familial diathesis for essential hypertension. The familial incidence of pre-eclampsia is set out in Table 4. If only one daughter of an eclamptic woman was tested by pregnancy, 24·7% had pre-eclampsia or eclampsia. If two daughters had pregnancies, one or both had pre-eclampsia in 35·8% of the families. With three daughters, at least one had pre-eclampsia in 46·7% of the families, and with four or five, the familial incidence was 66·7%.

Pregnancies in daughters-in-law

As controls, we have used the first pregnancies of 131 daughters-in-law of the eclamptic women, as representative women of comparable socio-economic status, age distribution, and period of time in which pregnancies occurred. They are fewer in number than the daughters, largely because of our lesser zeal and persistence in repeated requests for permission to see their hospital records.

Eight (6·1%) of the first pregnancies were said to have ended in abortion. Pre-eclampsia was diagnosed in eight, or 6·1% and four (3·1%) were considered to be borderline. Five (3·8%) had chronic hypertension, whereas only two of the daughters were known to have had it before the time of their first pregnancies. The death certificate of one daughter-in-law indicates that she died of eclampsia in her fourth pregnancy, but the record librarian of the hospital certifying her death insists that the women had not been a patient there.

Table 5. Observations recorded in hospital charts of primigravid granddaughters of eclamptic women

	Blood pressure					
	All readings hypertensive					
	Single recording	Two or more	Normal and hypertensive readings	No recording	One or more all normal	Totals
Cases	1	12	6	8	47	74
Proteinuria						
Negative or trace	1	0	3	1	19	24
One plus or more	0	8	0	0	5	13
No note about urine	0	4	3	7	23	37(50·0%)
Oedema						
None or slight	0	0	1	0	18	19
Present	0	5	2	1	5	13
No note about oedema	1	7	3	7	24	42(56·8%)
Proteinuria and oedema						
Neither	0	0	1	0	8	9
Both	0	4	0	0	2	6
One not noted	1	6	4	1	22	34(46%)
Neither noted	0	2	1	7	15	25(34%)
Diagnosis						
Borderline	0	0	3	0	0	3
Pre-eclampsia	0	12	0	0	0	12(16·2%)

Table 6. Familial incidence of pre-eclampsia in first viable pregnancies of granddaughters of eclamptic women

No of pregnancies for granddaughters	No. of granddaughters	No of families	Cases	Pre-eclampsia	
				% by granddaughters	% by families
1	20	20	4	20	20
2	16	8	1	6	13
3	12	4	0	0	0
4	8	2	1	13	50
7	7	1	2	29	100
11	11	1	4	36	100
Totals	74	36	12	16	22

Pregnancies in granddaughters

Pre-eclampsia was diagnosed in 12 of the 74 (16·2%) viable first pregnancies. Three others were considered borderline. Ten (13·5%) were known to have aborted their first pregnancies; two of them developed pre-eclampsia in their first viable gestations. There were two stillbirths, one in a normotensive pregnancy and one in a borderline case, both with placental abruption. Neither of the two neonatal deaths was associated with maternal pre-eclampsia.

Five of the 12 with pre-eclampsia have had later pregnancies; three were normotensive, one was mildly hypertensive without proteinuria or oedema, and in one the sole recording of blood pressure was 140/90 mmHg with two plus proteinuria and oedema of the hands and face.

Of 15 born through sons of eclamptic women, one had pre-eclampsia and one was borderline. Among the 59 born through daughters, 11 had pre-eclampsia and two were borderline. If we treat borderline as normal, the difference between the two ratios, 48:11 *vs* 14:1, is not significant, $P=0·24$ (Fisher's exact test).

As Table 5 shows, all of the 12 women with the diagnosis of pre-eclampsia had sustained (and acute) hypertension and at least eight had pro-

Table 7. Test of single recessive gene hypothesis: observed and expected numbers (in brackets) of the affected and normal individuals in various classes of relatives

		Daughters-in-law	Sisters	Daughters	Grand-daughters	Max. likelihood estimate of P (SE)	χ^2
Expected proportions	Normal	$1-P^2$	$1-1/4(1+P)^2$	$1-P$	$1-P(1+P)$		
	Affected	P^2	$1/4(1+P)^2$	P	$P(1+P)$		
Data of Chesley	Normal	69(70·10)	93(89·06)	139(139·20)	0	0·2556	0·71
et al. (1968)	Affected	6(4·90)	54(57·94)	48(47·80)	0	(0·0251)	(2 d.f.)
Data of this paper	Normal	54(50·53)	0	44(45·82)	62(62·50)	0·2489	0·96
	Affected	2(3·47)	0	17(15·18)	12(11·50	(0·0354)	(2 d.f.)
Combined data	Normal	123(122·60)	93(89·28)	183(185·21)	62(62·26)	0·2532	0·53
	Affected	8(8·40)	54(57·72)	65(62·79)	12(11·74)	(0·0205)	(3 d.f.)

d.f., Degrees of freedom.

teinuria of one plus or more; the urine was not tested in the other four, one of whom had a later normal pregnancy. Oedema was present in five, and there was no note as to its presence or absence in the other seven. The three classified as borderline had an interspersion of hypertensive and normotensive blood pressures and all had oedema, but their urines had not been examined.

The 74 granddaughters represented 36 families; at least one granddaughter had pre-eclampsia in 22% of the families, as shown in Table 6.

Eclampsia in other relatives

Our study of the familial factor began in 1935 when one of the eclamptic women told one of us (L.C.C.) that two of her sisters had died of eclampsia within 6 months of the time that she had had it. As time passed her two younger sisters had normal pregnancies, as did all three of their daughters. The patient's only daughter had severe pre-eclampsia, but has no daughters to carry on the tradition.

Five of the women said that their mothers had died of eclampsia and three told L.C.C. that their mothers had died in childbirth, causes unknown to them. One woman said that her grandmother had had eclampsia twice and died of it the second time; we could learn nothing of her mother's or aunts' pregnancies, but her daughter had severe pre-eclampsia with a stillbirth in her second pregnancy. One of her granddaughters has had pre-eclampsia in her first pregnancy. Thus, eclampsia or pre-eclampsia had occurred in at least four of five generations.

Seven daughters of the eclamptic women have had eclampsia, or one in 35. The incidence of pre-eclampsia or eclampsia in the first pregnancies of sisters of eclamptic women has been 37% and in 74 granddaughters, 16%.

The analysis of pregnancies of sisters was limited to those delivered in the Margaret Hague Maternity Hospital. One pair of sisters had eclampsia, which was fatal in one and accompanied by a stillbirth. Four other women having eclampsia in the Margaret Hague had sisters with eclampsia in other hospitals, which we confirmed by seeing their records.

Genetic analysis

The present and other data summarized in the introduction clearly show that eclampsia and pre-eclampsia have a strong familial incidence. Analysis of the pattern of inheritance presents a difficult problem in human genetics because the only known marker of the gene(s) is the development of pre-eclampsia. Such expression does not occur in half the population (men) and occurs only in the susceptible women who carry pregnancies to the third trimester.

Since the phenotype occurs only in pregnancy, a second difficulty is that we do not know whether we are dealing with the genotype of the mother, her fetus, or an interaction between the two. Here the comparison between blood relatives and relatives by marriage (in-laws) is valuable. For example if the maternal genotype alone is responsible, mothers of affected women should have a raised incidence but mothers-in-law should have the population incidence. If the fetal genotype alone is responsible, mothers

Table 8(a). Test of recessive hypothesis: expected proportions of families classified according to total number of daughters and number of pre-eclamptic daughters

Total no of daughters		Number of pre-eclamptic daughters 0	1	2	3
1	(a)	$1-P$	P		
	(b)	$1-P$	P		
2	(a)	$(1-P)^2+1/2P(1-P)$	$P(1-P)$	$P^2+1/2P(1-P)$	
	(b)	$(1-P)^2$	$2P(1-P)$	P^2	
3	(a)	$(1-P)^2+1/4P(1-P)$	$3/4P(1-P)$	$3/4P(1-P)$	$P^2+1/4P(1-P)$
	(b)	$(1-P)^3$	$3P(1-P)^2$	$3P^2(1-P)$	P^3

The proportions in the body of the data have been derived assuming that all eclamptic women are homozygous for the putative gene for pre-eclampsia, i.e. have genotype *h h* and that their partners are a random sample of the population i.e $(1-P)^2$ are *H H*, $2P(1-P)$ are *H h* and P^2 are *h h* where P is the frequency of the putative gene for pre-eclampsia. The expectations are derived under two assumptions: (a) = complete monogamy, i.e. partners pair for life; (b) complete promiscuity, i.e. partners are randomly exchanged after the production of one child We expect the reality lies between these two extremes, presumably nearer (a)

Table 8(b). Test of recessive hypothesis· expected and observed numbers of families of eclamptic women classified according to their total number of daughters and the number of pre-eclamptic daughters

Total no of daughters per family			No of pre-eclamptic daughters per family 0	1	2	3	4	5	χ^2	d.f.
1	Observed			70	23					
	Expected	(a)		69·45	23·55				0·02	1
		(b)		69·45	23·55				0·02	1
2	Observed			28	10	4				
	Expected	(a)		27·39	7·94	6·66			1·61	2
		(b)		23·42	15·88	2·69			3·71	2
3	Observed			8	4	3	0			
	Expected	(a)		9·07	2·13	2·13	1·67		2·47*	1*
		(b)		6·25	6·35	2·15	0·24		0·62*	1*
4	Observed			0	1	0	1	2	Numbers too small for analysis	
5	Observed			1	0	1	0	0		

*Obtained by pooling Class 0 with 3 and Class 1 with 2

d.f., Degrees of freedom.

None of the χ^2 is significant at the 5% level.

(a) = Expectations under the assumption of complete monogamy, and (b) = Expectations under the assumption of complete promiscuity. (See Table 8(b)).

P = 0·2532 (from Table 7).

and mothers-in-law should have the same incidence, since the fetus is equally related to both of its grandmothers. The data of Sutherland *et al.* (1981) indicate that the former is the case.

In order to test the simplest hypothesis, namely recessive inheritance, expectations in terms of the frequency of the hypothetical gene must be used. The incidence of pre-eclampsia is P^2 where P is the frequency of a postulated gene in a randomly mating population; *P*(0·2532) was calculated by maximum likelihood, based upon observed proportions shown in Table 7 (Rao 1952). Cases classed as borderline were treated as being normal, for two reasons. Although a few of them may have been pre-eclamptic, not enough information is available to sustain the diagnoses, and their exclusion may counterbalance, in part, erroneous diagnoses of pre-eclampsia.

The results of the analyses are shown in Tables

Table 9. Outcomes of first viable pregnancies of granddaughters of eclamptic women related to the natures of their mothers' first viable pregnancies.

First pregnancies of daughters or daughters-in-law of eclamptic women	No.	First pregnancies of granddaughters: Normal	Borderline	Pre-eclampsia	Information questionable
Normal	31	21	2	7*	1
Borderline	5	4	0	1	0
Pre-eclampsia	13	10	1	1	1
Information questionable	25	18	0	3	4
Totals	74	53	3	12	6

*One woman with pre-eclampsia was the daughter of a woman whose first pregnancy was normal, but who had severe pre-eclampsia with still birth in her second gestation.

7, 8a, and 8b. Both the proportions of pre-eclamptic women in various classes of relatives of eclamptic women (Table 7) and within siblings in families with more than one daughter tested by pregnancy (Tables 8a and 8b) are in good agreement with the predictions made by the hypothesis that a single recessive gene acting in the mother determines pre-eclampsia. The low incidence in daughters-in-law (Table 7) argues against the fetal influence i.e. that the son of the eclamptic woman is contributing genes to the fetus which causes his spouse to suffer pre-eclampsia. Likewise the close agreement between the gene frequencies calculated for the 1935–1968 data and for the 1969–1984 data suggests that the diagnoses, however difficult they may be to make from the often inadequate information available, have been consistent over the half century during which the data were collected.

For the purposes of the analysis, granddaughters were treated as a single group, irrespective of whether their mothers had pre-eclampsia or not, because their numbers are comparatively small. The expectation for the frequency of pre-eclampsia in granddaughters whose mothers had pre-eclampsia is P, and for granddaughters whose mothers were normotensive it is 1/2P; the observed incidences were actually 1 in 13, and 7 in 31, respectively (Table 9). While these incidences seem at variance with the expectation, based upon P = 0·2532, they probably are attributable to small numbers. The exact binomial probability for the agreement of the 1 in 13 with the corresponding expectation is 0·24 (two tailed test), and χ^2 for the agreement between observed and expected for the 7 in 13 is 2·76 (P>0·05).

Hypertension, proteinuria, and oedema are in reality quantitative characters. The diagnosis of pre-eclampsia is essentially the imposition of arbitrary cutoff points in those continuous variables, largely in order to classify patients for the purposes of clinical management. Such disorders have been treated as 'threshold' characters by Falconer (1965, 1967); those above certain thresholds for the variables in question have the disease, those below it do not. His treatment allows estimation of the heritability of the condition and the results of that type of analysis for pre-eclampsia are shown in Table 10.

Discussion

The diagnosis of pre-eclampsia

The unique strength of the present study is that all of the probands had eclampsia, the diagnosis of which is far more secure than is that of pre-eclampsia. The weakness lies in the diagnosis of

Table 10. Heritability values for pre-eclampsia*

Class of relative	Heritability	Standard error (%)
Sisters	120	13·0
Daughters	88	12·4
Granddaughters	105	42·1

Data from Table 7.
*Calculated by method of Falconer (1965, 1967).

pre-eclampsia in the sisters and descendants of the eclamptic women, and in the controls.

All studies of pre-eclampsia are plagued by erroneous diagnoses, which are common. The Chicago Lying-in Hospital has been a leading centre for research on hypertension in pregnancy for half a century and there, if anywhere, careful diagnoses must be made. In the 1960s and 1970s, renal biopsies were taken from many of their hypertensive patients. Fisher *et al.* (1981) retrospectively compared the results of histological and electron microscopic examination of the biopsies with the clinical diagnoses. In 104 primiparae with the clinical features of pre-eclampsia, 76% had only the glomerular endotheliosis thought to be characteristic of 'true' pre-eclampsia, 8% had endotheliosis combined with features of other renal diseases and 16% had other renal diseases with no endotheliosis. By contrast, in 72 multiparae diagnosed clinically as pre-elcamptic, 24% had endotheliosis alone, 14% had both endotheliosis and other renal disease features, 51% had only other renal diseases, and 8% were histologically normal. Clearly, for the purposes of genetic analysis the diagnosis must be based upon first pregnancy data. Even then there is a 16% chance of misclassification, if the presence of endotheliosis is taken as the basis of classification.

Fisher *et al.* (1981) also demonstrated that the degree of proteinuria in pure pre-eclampsia showed a linear correlation with the degree of endotheliosis. We have been reluctant to make the diagnosis of pre-eclampsia in the absence of proteinuria, but the urines of so many patients had not been examined that we have risked errors. Proteinuria is almost always a late sign in the course of the disorder and abates rapidly after delivery. Again, we have risked error in making the diagnosis of pre-eclampsia in women whose urine did not show protein at one to several days after delivery. Most of the diagnoses may have been salvaged by the patients having later normotensive pregnancies.

Genetic analysis

The genetic analysis indicates that the data are compatible with a single gene model. Despite the close fit between prediction of the recessive model and the observed data, the model should at present be regarded only as a useful working one. The inevitable lack of expression of the phenotype in men and women who have not been pregnant imposes severe limitations upon our capacity to test critically even the simplest hypotheses with the classical methods of pedigree analysis we have used. Cooper & Liston (1979) and Sutherland *et al.* (1981) found that the data for mothers and daughters from a Scottish population gave good agreement with the recessive model, but that the incidence in sisters of the index cases was less than predicted. That could be an indication that the model is, at best, an oversimplification, although their probands were pre-eclamptic rather than eclamptic women. Thus in view of the difficulties of diagnosis, referred to above, it is possible that their probands were heterogeneous, with some not suffering 'true' pre-eclampsia.

In all other respects the Aberdeen data and ours tell a very similar story. The putative gene frequency for Aberdeen is 0·237 compared to our 0·253. Both sets of data show a population incidence for in-laws, ruling out a significant genetic contribution from the fetus. Specifically the incidence in our daughers-in-law, 8/131 = 6·1%, agrees well with the figure of 5·6% in the overall Aberdeen population (Cooper & Liston 1979). The mother-daughter correlation is very similar in the two sets of data.

Our data on incidence in granddaughters, though comparatively few, are the first of their kind to be published. It is noteworthy that as predicted by the hypothesis, grandaughters of affected females born through sons and daughters have similar incidences. Moreover granddaughters of affected females born through pre-eclamptic and normal mothers also have the predicted incidences.

Since the individual characteristics—blood pressure, proteinuria, and oedema—that go to make up the condition are quantitative rather than qualitative, it could be argued that the methods of quantitative genetics are more appropriate here. The data are collected in such a form that only Falconer's (1965, 1967) treatment as a threshold character is possible. The heritability estimates so obtained are high, which confirms the impression from the analysis based upon the single gene model, that in these data the susceptibility is largely genetic in origin, with the environment playing a small, perhaps negligible role. It is of particular significance that the constellation of raised blood pressure, raised urinary protein levels, and raised oedema can be transmited through three generations. That suggests that they are each caused by one common underlying factor.

Because of the unavoidable restrictions the data place upon genetic analysis, it is doubtful whether the collection of further clinical data can advance our understanding of the genetic basis of the disease; the exception to that would be the collection of data in twins, which has yet to be conducted on a sufficient scale. The most fruitful future investigations along genetic lines are likely to be at the biochemical and molecular levels. If, as has been conjectured many times, the condition has an immunological basis, then associations and linkages with immunological markers should be sought, either in populations or through the affected sib pair method (Thomson 1981). In that way, the ultimate goal of identifying the particular DNA sequences that give rise to the condition may be attained.

Finally, it must be recognized that, while the set of data of this paper are in very good agreement with the single gene hypothesis, this cannot explain all cases of pre-eclampsia. Pre-eclampsia, defined in the same way as we have, is much more common in twin pregnancies, in diabetes, and in the presence of hydatidiform moles or fetal hydrops (reviewed in Chesley 1978). These cases cannot be explained by our single gene hypothesis and must have some other cause. They could also be used to argue that a multifactorial hypothesis for all cases of pre-eclampsia is at least plausible. We do not seriously dispute that view. We have emphasized the single gene hypothesis for heuristic reasons; in the present state of knowledge, it seems to us that a search for single genes that confer susceptibility is the most likely way of advancing our understanding of basic nature of the condition.

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Amniotic fluid concentrations of secreted pregnancy-associated endometrial α_1- and α_2-globulins (α_1- and α_2-PEG)

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Summary. The levels of pregnancy-associated endometrial α_1- and α_2-globulins (α_1- and α_2-PEG), the two major proteins synthesized and secreted by the endometrium *in vitro*, have been assayed in 210 amniotic fluid specimens obtained at termination of pregnancy or by amniocentesis, or at delivery. α_1-PEG was undetectable until week 10 and thereafter rose to peak levels between weeks 20 and 24. Levels fell 15-fold by week 35 but substantial amounts were still present at parturition. α_2-PEG was present at highest levels during early pregnancy, at weeks 6–15, but thereafter levels rapidly fell until during weeks 31–42 α_2-PEG was detectable in only 3 of 25 specimens. During weeks 15–20, when α_2-PEG levels fell and α_1-PEG levels rose, a high correlation was observed between the week of gestation and the log of the ratios of the concentration of these proteins. These observations provide the opportunity to assess the role of endometrial and decidual dysfunction in the aetiology of pregnancy disorders.

Differentiation of the endometrium begins during the luteal phase of the menstrual cycle, with glandular epithelial secretion and decidualization of the stroma. This process is extended if pregnancy intervenes and is maximal during the first trimester (Robertson 1981). Our understanding of its role in establishing and maintaining pregnancy and of the role in pregnancy failure may be facilitated by the identification and study of specific secretory endometrial and decidual products (O'Grady & Bell 1977; Bell 1985). Indeed, in rodents functions ascribed to the decidualized endometrium have been associated with secretory proteins (Bell 1983*a*, *b*).

We have identified 17 proteins synthesized *de novo* secreted *in vitro* by the endometrium during the menstrual cycle and the first trimester of pregnancy, but approximately 60% of radiolabelled amino acid is incorporated into only two proteins during early pregnancy (Bell *et al.* 1985*a*, 1986). These two proteins, termed pregnancy-associated endometrial α_1- and α_2-globulins, α_1- and α_2-PEG (Bell *et al.* 1985*b*) represent the major secretory proteins of the pregnancy endometrium. α_2-PEG also represents the major secretory protein of the secretory endometrium during the menstrual cycle and may represent the human analogue of rabbit

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uteroglobin (Bell *et al.* 1986). α_1-PEG does not bind concanavalin A and is a protein of M_r 36 K (gel filtration) or M_r 32 K (gel electrophoresis) possessing two pI forms. α_2-PEG is a dimeric glycoprotein of M_r 56 K, subunit M_r 28 K, which, however, exhibits multiple pI forms and size polymorphism (Bell *et al.* 1985*b*). The in-vitro rates of synthesis and secretion of these proteins alter dramatically during early pregnancy with α_2-PEG being the major secretory protein at 6 weeks and α_1-PEG the major product at 12–15 weeks. This suggests that they have different origins within the endometrium and that they may reflect different endometrial functions.

A bispecific antiserum prepared against cytosol of pregnancy endometrium, which reacted against α_1- and α_2-PEG, previously detected high levels of immunoreactive α_1- and α_2-PEG in amniotic fluid (Bell *et al.* 1985*b*). Subsequently, this immunoreactivity was found to represent authentic α_1- and α_2-PEG (unpublished observations). In this study, α_1- and α_2-PEG levels have been determined by immunochemical methods in amniotic fluid specimens obtained during pregnancy.

Materials and methods

Specimens

Amniotic fluid specimens were obtained from three groups of patients. Specimens at 6–14 weeks were obtained from patients attending the Leicester Royal Infirmary for therapeutic termination of pregnancy. Fluid was aspirated transcervically after dilatation of the cervix, just before evacuation of the uterus. Specimens at 14–21 weeks were obtained from patients who underwent amniocentesis for alpha-fetoprotein screening, these fluids were obtained from the Supraregional Protein Reference Unit, Department of Immunology, Royal Hallamshire Hospital, Sheffield, and only amniotic fluids which contained normal AFP levels were used. During this period a minimum of 20 specimens was assayed at each week of gestation. The other amniotic fluid specimens were obtained during normal labour, and during elective caesarean section. Amniotic fluids were centrifuged at 1000 *g* for 20 min and stored at −20°C although the proteins in amniotic fluid appeared stable if stored at 4°C for 3 months.

Antisera and reference antigens

Monospecific antisera against α_1-PEG and α_2-PEG were raised in adult male rabbits (New Zealand White) using α_1-PEG purified from in-vitro culture medium of first trimester pregnancy endometrium, and α_2-PEG purified from cytosols of first trimester pregnancy endometrium as described previously (Bell *et al.* 1985*b*).

Immunoelectrophoretic techniques

α_1- and α_2-PEG were assayed in amniotic fluids using the monospecific antisera in a rocket immunoelectrophoretic assay (Laurell 1972) in 1% (*w*/*v*) agarose in 0·06 M-barbital buffer (pH 8·6) with a voltage gradient of 100 V for 18 h on 10 × 10 cm glass plates backed by Gel bond. Precipitin lines were stained with Coomassie Brilliant Blue G250 after washing with distilled water.

For the α_1-PEG assay the agarose contained 2% rabbit and anti-α_1-PEG antiserum and wells contained 5 µl of amniotic fluid diluted up to 1:16. α_1-PEG partially purified from in-vitro incubation medium of cultures of pregnancy endometrium was employed for a standard (Bell *et al.* 1985*b*). The sensitivity of the assay was 2 µg/ml amniotic fluid and the interassay coefficient of variation was 5%.

For the α_2-PEG assay the agarose contained 3·5% rabbit anti-α_2-PEG antiserum and wells contained 10 µl of amniotic fluid. α_2-PEG partially purified from cytosols of pregnancy endometrium was employed as a standard. The sensitivity of the assay was 2 µg/ml amniotic fluid and the interassay coefficient of variation was 5%.

Protein estimation

The colorimetric method of Bradford (1976) was used to determine total protein content using human serum albumin as a reference standard.

Statistical analysis

The data was log transformed before calculation of mean and standard errors. Comparison of data was performed using Student's *t*-test.

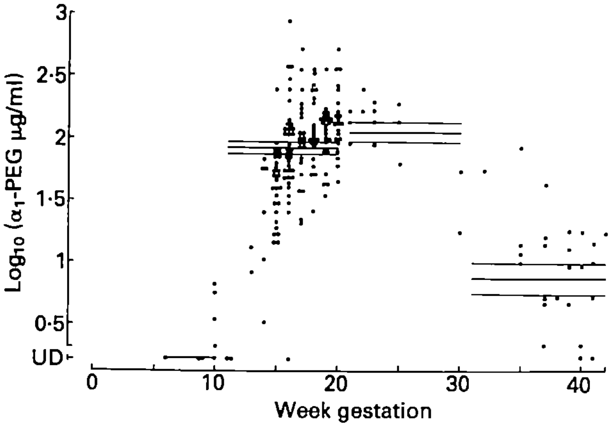

Fig. 1. Levels of α_1-PEG in amniotic fluid during gestation. Bars represent mean ± 1 SEM of levels over period enclosed by bar. UD, Undetectable levels.

Results

Amniotic fluid levels of α_1-PEG during gestation

Figure 1 shows the concentrations of α_1-PEG in 210 amniotic fluid specimens obtained throughout gestation. As the results were not normally distributed the concentrations were plotted as their log value. Comparison of grouped data demonstrated a 128-fold increase in concentration from 6–10 weeks to 11–20 weeks ($P<0{\cdot}001$) and a further small but not significant increase by 21–30 weeks. A dramatic 14·8-fold fall in values was observed by 31–41 weeks ($P<0{\cdot}001$) but these concentrations were still 11·5-fold higher than those detected at 6–10 weeks ($P<0{\cdot}01$). α_1-PEG was first detectable at 10 weeks and rapidly increased to peak levels at 20–24 weeks and thereafter fell until 35 weeks. During this period, weeks 10–35, α_1-PEG was undetectable in only 4 of 187 specimens. No statistical difference was observed between weeks 35 and 42 and during this period, α_1-PEG was detected in all, except two, of 24 specimens.

Amniotic fluid levels of α_2-PEG during gestation

Figure 2 shows the concentrations of α_2-PEG in 210 amniotic fluid specimens obtained throughout gestation. These values also did not exhibit a normal distribution therefore levels were expressed as their log values. Comparison of

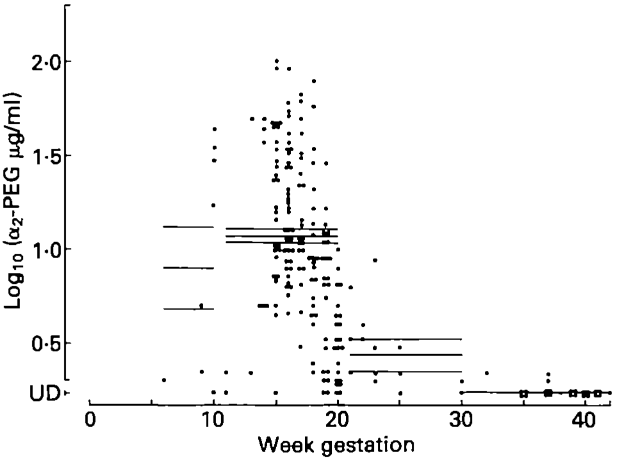

Fig. 2. Levels of α_2-PEG in amniotic fluid during gestation. Bars represent mean ± 1 SEM of levels over period enclosed by bar UD, Undetectable levels.

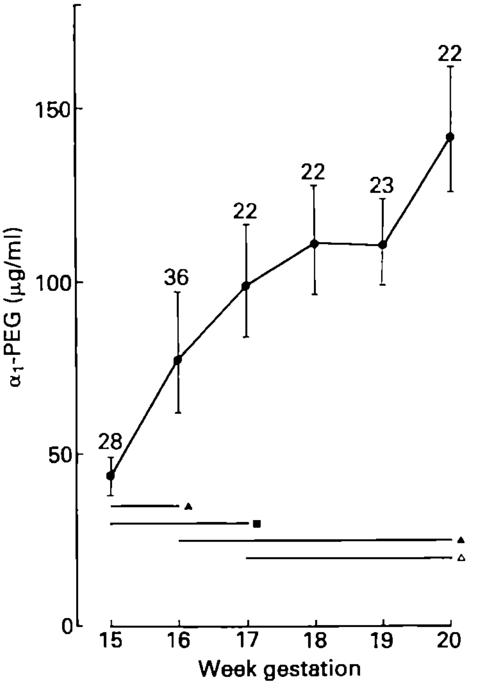

Fig. 3. Levels of α_1-PEG between weeks 15 and 20 Levels expressed as mean ± 1 SEM. Statistics were performed on log transformed data Comparison of data was obtained employing the Student's *t*-test. Bars indicate groups that were compared and levels of significance were as follows. (■) $P<0·001$; (□) $P<0·02$; (▲) $P<0·05$; (△) NS.

grouped data demonstrated highest values during weeks, 6–10 and 11–20 (no significant difference) with a dramatic 4·4-fold fall in levels by 21–30 weeks ($P<0·001$). Levels fell by a further 2·5-fold by 31–42 weeks ($P<0·001$). α_2-PEG was first detectable at 6 weeks. However, no gradual rise in levels was observed since levels in specimens positive during 6–14 weeks were not significantly different from those at 15 weeks. Levels fell 4·9-fold from weeks 15 to 20 ($P<0·001$), and from weeks 25 to 42 α_2-PEG was detectable in only 6 of 30 specimens.

Relation between α_1-PEG and α_2-PEG levels during weeks 15–20

The period during which specimens were available by amniocentesis corresponded to a period of rapid alteration in α_1-PEG and α_2-PEG levels (Figs 3 and 4). As shown in Fig. 3 α_1-PEG levels increased 3·3-fold from weeks 15 to 20 whereas as shown in Fig. 4 levels of α_2-PEG fell during the same period and most steeply, i.e. 4·5-fold, between weeks 17 and 20. When the log of the ratios of the mean levels of α_1-PEG and α_2-PEG, calculated from Figs 3 and 4, was plotted against week of gestation, a linear relation was observed ($y = 0·235, x - 3·1, r = 0·9909, P<0·001$). Therefore, the log of α_1-PEG/α_2-PEG values was calculated for all amniotic fluid specimens. As shown in Fig. 5 a similar linear relation was obtained for these values between weeks 10 and 20 ($y = 0·215, x - 2·78, r = 0·9928, P<0·001$) reflecting the dramatic differential alteration of α_1- and α_2-PEG levels during this period.

Discussion

This study has demonstrated that there is dramatic difference between the amniotic fluid profiles of the two major secretory proteins of the endometrium during normal pregnancy (Bell *et al.* 1985*a*, *b*, 1986). α_2-PEG levels are highest during weeks 10–15 and are undetectable during the late third trimester whereas α_1-PEG levels increase from week 10, are maximal at weeks 20–24, and are still substantial during the third trimester. This switch in the levels of these endometrial proteins is most marked during weeks 10 to 20 when the α_1-PEG/α_2-PEG ratio changes from 0·2 to 35·5.

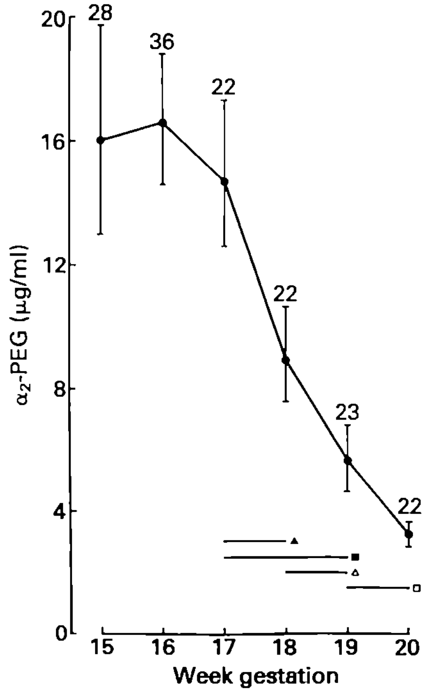

Fig. 4. Levels of α_2-PEG between weeks 15 and 20. See legend Fig. 3 for details.

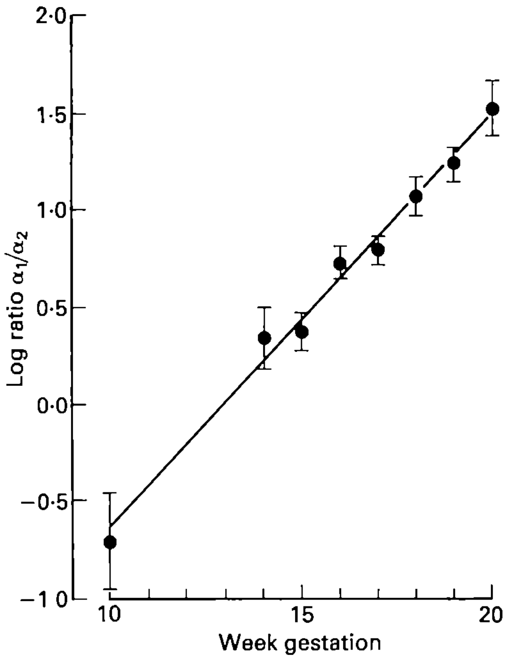

Fig. 5. Ratios of α_1-PEG to α_2-PEG levels in amniotic fluid specimens between 10 and 20 weeks gestation. The log of the ratios of α_1-PEG to α_2-PEG in amniotic fluid specimens was calculated and results were expressed as mean ± 1 SEM. Line obtained by linear regression analysis.

Although the tissue origin of these amniotic fluid proteins has not been unequivocally proven, only the female endometrium has been shown to synthesize and secrete these proteins *in vitro* (Bell *et al.* 1985*a*) and this suggests that it is the site of origin of these amniotic fluid proteins *in vivo*.

Pregnancy endometrium *in vitro* exhibits a similar switch from α_2-PEG to α_1-PEG synthesis and secretion at different periods of gestation although this switch occurs approximately 5–6 weeks earlier in endometrium than amniotic fluid (Bell *et al.* 1985*a*). This delay in appearance of endometrial proteins in amniotic fluid may result from a requirement for apposition and fusion of the amnion and chorion. Transport of endometrial prolactin into the amniotic fluid requires fusion of the endometrium to the amniochorion (McCoshen *et al.* 1982). The equivalent delay in the fall of amniotic fluid levels after the fall in endometrial synthesis and secretion may reflect the half-life of the proteins in amniotic fluid.

The different profiles of these proteins in amniotic fluid supports the suggested origins of these proteins within the endometrium. α_2-PEG synthesis appears principally associated with the decidua spongiosa layer, the distinctive cellular type of this layer being the secretory glandular epithelium. This cellular origin is supported by the demonstration of synthesis by the mid-secretory endometrium during the menstrual cycle (Bell *et al.* 1986). The glands of the spongiosa involute after the first trimester, and therefore, the declining synthesis and amniotic fluid levels may reflect this phenomenon. In contrast, α_1-PEG synthesis appears to be associated with the decidual cell-containing decidua compacta, a tissue present throughout pregnancy (Robertson 1981).

The fact that the observed fall in amniotic fluid levels of α_1-PEG corresponds to a period of rapid increase in amniotic fluid volume, i.e. weeks 24–34 suggests that the rate of α_1-PEG synthesis and secretion is maintained during this period. The concentration profile of α_2-PEG in amniotic fluid is similar to the specific activity profiles of α-1,4-glucosidase and heat-labile alkaline phosphatase (Sutcliffe & Brock 1972; Sutcliffe *et al.* 1972) and may reflect a similar endometrial glandular origin. The majority of amniotic fluid proteins, however, reach maximum levels between 20 and 30 weeks and are of maternal serum origin, which is similar to the profiles of endometrially-derived α_1-PEG and diamine oxidase. It is interesting to note that diamine oxidase is also suggested to originate from endometrial decidual cells (Weisburger *et al.* 1978).

All the products demonstrated to be synthesized and secreted by the endometrium during pregnancy have been detected at highest concentrations in amniotic fluid, i.e. prolactin, diamine oxidase, 'progestagen-dependent endometrial protein' (PEP) (Joshi *et al.* 1980), α_1- and α_2-PEG, and thus this may reflect a general principle that endometrial secretory products are principally transported across the amniochorion into the amniotic fluid. This would imply that pregnancy-associated plasma protein A (PAPP-A), recently suggested to be derived from the endometrium (Bischof *et al.* 1984), is not derived from this tissue since amniotic fluid levels of this protein are much lower than in maternal serum (Bischof *et al.* 1982). The functions of α_1- and α_2-PEG within the amniotic fluid is unknown although the dramatically different profiles of synthesis, secretion and accumulation of α_2- and α_1-PEG in the amniotic fluid may suggest they fulfil different functions at different stages of pregnancy, i.e. α_2-PEG during the first trimester and α_1-PEG during the second and third trimester.

Consideration must be given to the possible relation between the endometrially-derived proteins and other proteins detected in the amniotic fluid. Of direct relevance are those proteins isolated from the placenta since chorionic α_1-microglobulin (CAG-1) (Petrunin *et al.* 1978), placental protein 12 (PP 12) (Bohn *et al.* 1982) and α_1-PEG appear to be immunochemically related (Bell & Drife 1986), and also chorionic α_2-microglobulin (CAG-2), placental protein 14 (PP 14) and α_2-PEG to be immunochemically related (Bell & Drife 1986), in spite of their reported physicochemical dissimilarity. It is of interest that Rutanen *et al.* (1985) showed that PP 12 was synthesized and secreted by decidua at term. CAG-2/PP 14 has been detected in amniotic fluid and although detailed changes in concentration during gestation have not been investigated, similar to α_2-PEG, the highest levels in amniotic fluid have been detected during the first trimester (Tartarinov *et al.* 1980; Bohn *et al.* 1982). Similar to α_1-PEG levels highest levels of PP 12 have been detected in amniotic fluid during the second trimester (Bohn *et al.* 1982; Rutanen *et al.* 1982) although this has not been confirmed for CAG-1 (Tartarinov *et al.* 1980). α_2-PEG is also probably related to PEP since highest levels of this endometrial protein have been reported between weeks 15 and 18 (Joshi *et al.* 1980).

The mechanism of transport of these proteins across the amnion and chorion is unknown, but specific receptors may exist on the chorion since they have been demonstrated for prolactin, another endometrial product transported into amniotic fluid (Herington *et al.* 1980). Defects in the levels of these chorionic prolactin receptors have been linked with chronic polyhydramnios (Healy *et al.* 1985) and information about the function of α_1- and α_2-PEG may be obtained if clinical conditions associated with defects in their receptor levels could be identified. The profiles of levels of α_1- and α_2-PEG in amniotic fluid during normal gestation established in this study will now provide the opportunity to determine levels of these proteins in abnormal pregnancy. Such investigations should determine whether assays of these endometrially-derived proteins will be useful in clinical diagnosis and shed light upon their function during normal pregnancy.

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Comparison of different antibody preparations against pregnancy-associated plasma protein-A (PAPP-A) for use in localization and immunoassay studies

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Summary. Four antibody preparations against pregnancy-associated plasma protein (PAPP-A) were compared in order to find an explanation for the contradictory results published on tissue localization, clinical usefulness and biological function of PAPP-A. One of the preparations studied was a rabbit anti-PAPP-A antiserum which has been offered for general scientific use (Bischof *et al.* 1979). Only the IgG fraction of anti-PAPP-A antisera which appeared to be monospecific and had been further absorbed with fetal connective tissue gave specific uniform staining of the cytoplasm of the syncytiotrophoblast exclusively. Circulating PAPP-A could not be detected by RIA employing this IgG preparation in the non-pregnant state, or before 18 days after conception. Circulating PAPP-A could be detected in all seven pregnant women studied within 4 weeks after conception. Identical results were obtained with a commercially available IgG fraction against PAPP-A.

Pregnancy-associated plasma protein-A (PAPP-A) is a high molecular weight glycoprotein (750–800 kD) with alpha-2 electrophoretic mobility which has been identified in and extracted from the peripheral blood in the third trimester of pregnancy (Lin *et al.* 1974). However, as there is little agreement on the biological activity and site of synthesis of this molecule, some aspects of PAPP-A are the subject of considerable debate (Lin & Halbert 1976; Wahlström *et al.* 1981; McIntyre *et al.* 1981; DuBerg *et al.* 1982; Gosseye & Fox 1984; Schindler *et al.* 1984; Tornehave *et al.* 1984). First, although it has been tempting to speculate that the major action of PAPP-A is expressed in immunological and/or coagulation mechanisms, the most convincing arguments have been put forward for its activity against granulocyte elastase (Sinosich *et al.* 1982*a*). Second, the weight of evidence for the site of synthesis of PAPP-A has depended on studies of immunohistochemical localization

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using indirect immunofluorescence and enzyme bridge techniques demonstrating the presence of PAPP-A in the tissue. These reports show little agreement and PAPP-A has been shown to be localized in the apical rim of the syncytiotrophoblast (Wahlström *et al.* 1981; Bischof *et al.* 1984*a,b*; Schindler *et al.* 1984); predominantly in the decidualized endometrium (DuBerg *et al.* 1982); in the cytotrophoblastic cells only (Dobashi *et al.* 1984), or in common with other proteins of placental origin (hPL, hCG, SP-1) in cytoplasm of the syncytiotrophoblast (Gosseye & Fox 1984; Tornehave *et al.* 1984).

Finally, although there is general agreement that PAPP-A-like material has been identified in pre-ovulatory follicular fluid and seminal plasma (Bischof *et al.* 1983*a, b*; Sinosich *et al.* 1984; Sjöberg *et al.* 1984, 1985; Stanger *et al.* 1985; Westergaard *et al.* 1985), evidence for the presence of PAPP-A in the peripheral blood in the non-pregnant state is not in such accord, the majority of centres having identified circulating PAPP-A 4 weeks after conception (Anthony *et al.* 1983; Pinto-Furtado *et al.* 1984; Sinosich *et al.* 1982*b*; Sjöberg *et al.* 1984; Westergaard *et al.* 1983).

This study has been undertaken to establish whether some of the discrepancies in these results are simply a consequence of differences in the various antibody preparations used and/or differences in the applied immunochemical techniques.

Materials and methods

Anti-PAPP-A preparations

The reference procedure for the preparation of anti-PAPP-A antibodies was the one routinely performed at the University of Odense, where PAPP-A for immunization is purified by a combination of heparin affinity chromatography and size chromatography as described by Davey *et al.* (1983). In brief, following venesection of the rabbits, the antiserum was absorbed to monospecificity by differentiated absorption with serum obtained from non-pregnant women (Folkersen *et al.* 1978, 1981). This was followed by an absorption with minced fetal connective tissue (0·5 g/ml of antiserum) to remove specificities against fetal and connective tissue antigens. Hereafter the IgG fraction was isolated by a combination of $(NH_4)_2SO_4$ precipita-

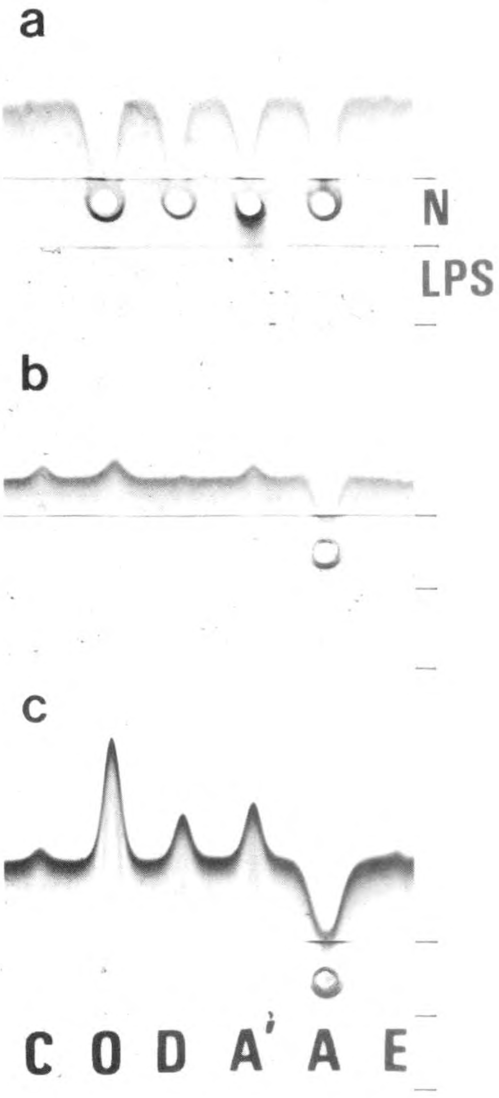

Fig. 1. Line immunoelectrophoretic analysis of antibody preparations for the presence of specificities against PAPP-A (a), PZP (b) and α_2M (c). The upper gel areas contained anti-PAPP-A (a), anti-PZP (b) and anti-α_2M (c) antibodies. The gels indicated as N were neutral gels in which wells for antibody preparations were cut: C is the control preparations, O, D, A' and A are four different anti PAPP-A preparations (see text), and the well indicated as E was empty. LPS: this gel contained late pregnancy serum. Negative (i.e. downward) deflection of the line precipitate indicates the presence of the corresponding specificity in the antibody preparations.

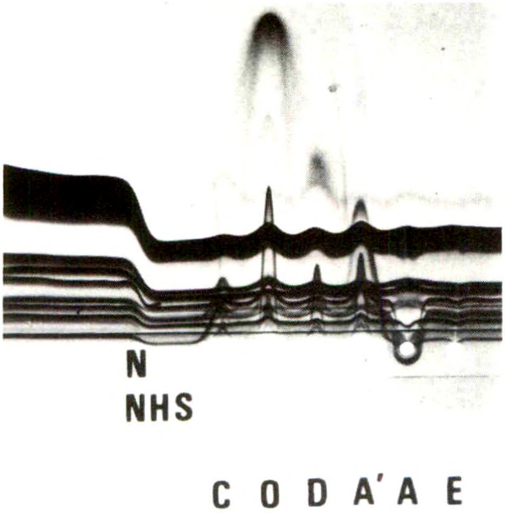

Fig. 2. Line immunoelectrophoresis with rabbit-anti whole human IgG in the upper gel area. NHS: this gel contained serum obtained from non-pregnant women. The design of the technique is identical to that of Fig. 1.

tion and ion exchange chromatography. This preparation is referred to as preparation O. Four other anti PAPP-A preparations were examined.

Preparation A. This was the crude rabbit anti-PAPP-A antiserum kindly supplied by Dr P. Bischof, Geneva, which was originally produced in Aberdeen and offered for scientific assessment (Bischof *et al.* 1979).

Preparation A'. This was the IgG fraction produced after preparation A was further processed (absorption procedures and isolation of the IgG fraction) according to the procedures described above for preparation O.

Preparation D. This was the commercially available rabbit anti-PAPP-A IgG fraction (Dakopatts, Copenhagen, Denmark).

Preparation C. This was a control IgG fraction which originated from the same anti-PAPP-A antiserum as preparation O and was processed in the same way as preparation O, except that the differentiated absorption procedure used late pregnancy serum.

Tissues and tissue preparation

Normal trophoblastic tissues were obtained at term after vaginal delivery and during hysterectomy (gestational age 60 days). Decidualized endometrium was obtained at week 8 of gestation during therapeutic abortion. All tissues were immersion fixed in 4% (*w*/*v*) paraformaldehyde for 4–6 h, washed in phosphate buffered saline for 24 h at 4°C, dehydrated in ethanol and cleared in toluene before being embedded in Paraplast at 56°C (Chemnitz *et al.* 1984; Tornehave *et al.* 1984). All sections (5 μm) were placed on ethanol-cleaned microscope slides.

Staining procedure

The immunohistochemical staining procedure was performed as described previously (Chemnitz *et al.* 1984; Tornehave *et al.* 1984) with and without pre-treatment of the tissue sections with 0·1% (*w*/*v*) trypsin in 0·1% $CaCl_2$, pH adjusted to 7·8, for 10 min. All antibody preparations (O, A, A^1 and D) were adjusted to identical anti-PAPP-A titres before they were applied for localization study. The anti-PAPP-A titres of the different preparations examined were assessed by the antigen consumption electroimmunoassay described by Folkersen *et al.* (1978).

Line immunoelectrophoresis

The design of the line immunoelectrophoretic technique used in the evaluation of antibody specificity is shown in Fig. 1 and the technique was performed as described previously (Krøll 1983). The antibodies applied in the antibody containing gel were rabbit anti-PAPP-A IgG (Preparation O), rabbit anti-pregnancy zone protein IgG (Folkersen *et al.* 1978), rabbit anti-alpha-2 macroglobulin (α_2M, Dakopatts, Copenhagen, Denmark) or rabbit anti-whole human serum IgG (Dakopatts).

Subjects and blood samples

Venous blood samples ($n=195$) were obtained from 29 women attending the infertility clinic at Odense University Hospital for artificial insemination by donor (AID) during 79 ovarian cycles. Blood samples were collected immediately after AID treatment which was performed 24–48 h after a significant rise in basal body temperature and appropriate cervical

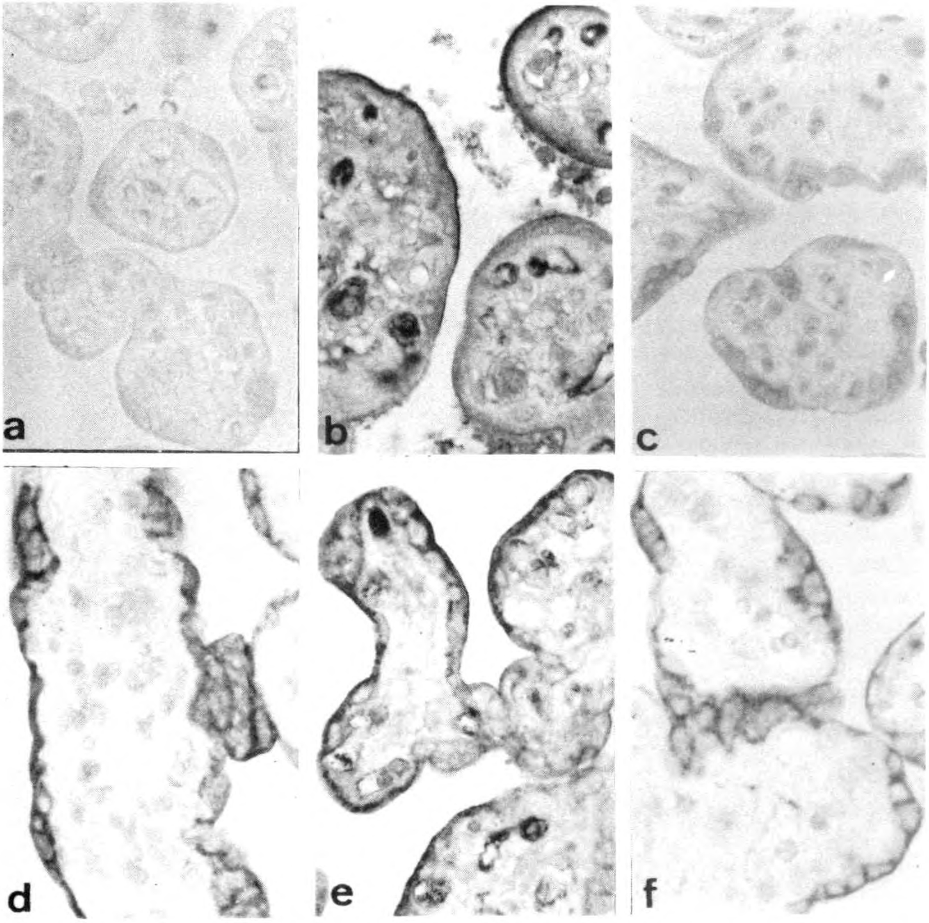

Fig. 3. Immunohistochemical examinations of anti-PAPP-A preparations on paraformaldehyde fixed placental tissue. The staining reaction for the antibody preparations O (a, d), A (b, e) and A′ (c, f) are shown. Tissue sections shown in (a), (b) and (c) were without and sections in (d), (e) and (f) with tryptic pre-treatment (see text) × 400.

mucus changes, and at weekly intervals until menstruation occurred ($n=22$) or 10 weeks gestation, and less frequently thereafter ($n=7$). Serum was separated within 2 h of collection, aliquoted and stored at −70°C until assayed. PAPP-A was measured by radioimmunoassay as described previously (Pinto-Furtado *et al.* 1984). Preparations O or D were used in the assay, the detection limit being 3 m-i.u./l (WHO reference material 78/610). Preparations A and A′ were not analysed in the RIA procedure.

Results

Figure 1 shows the line immunoelectrophoretic analysis of the different preparations for the presence of antibodies against PAPP-A (Fig. 1a), pregnancy zone protein (PZP; Fig. 1b) and alpha-2 macroglobulin (α_2M; Fig. 1c). Whereas all preparation except the control preparation (C) contained specificities against PAPP-A, only preparation A contained specificities against PZP and α_2M as indicated by the negative deflection of the line precipitate. Further analysis of the preparations by line immunoelectrophoresis using anti-whole human serum IgG (Fig. 2) revealed that preparation A, in addition to the contaminating specificities against α_2M and PZP, contained another four specificities against proteins unrelated to PAPP-A. One of these proteins was identified as beta-lipoprotein. All contaminating specificities were removed when this preparation was further processed (as described) to produce preparation A′. Preparations O, D and A′ appeared to be monospecific having antibody specificities against PAPP-A only.

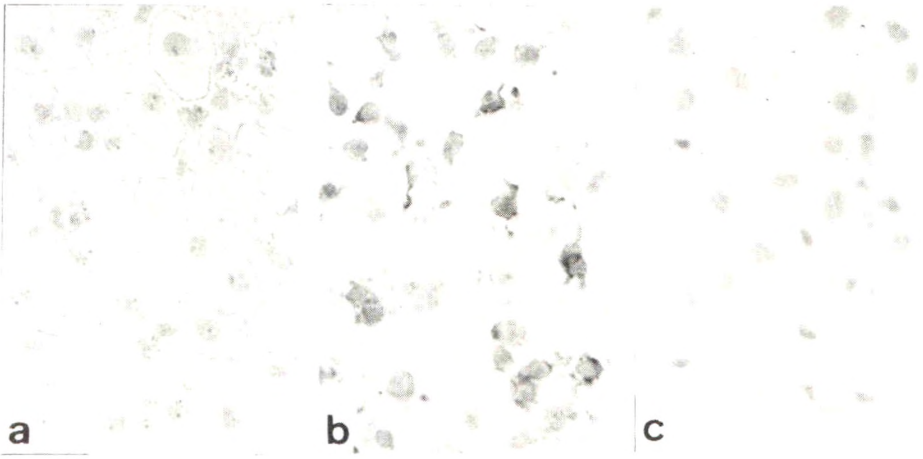

Fig. 4. Immunohistochemical examination of anti-PAPP-A preparations on decidualized endometrium. All tissue sections shown are pre-treated with trypsin. The staining reaction for preparation O (a), A (b) and A′ (c) are shown (see text) × 400.

Figure 3 shows the results of immunohistochemical staining of chorionic tissue obtained at term. Unless trypsin pre-treatment was used, preparation O (incubation for 30 min at 37°C) failed to produce an obvious staining of this tissue. By contrast, preparation A showed strong staining of all tissue elements including the core of the villus. Furthermore, the staining of the trophoblast was most pronounced in the apical rim. When preparation A was further processed the resulting preparation (A′) did not produce significant staining. Preparation D (results not shown) caused slight staining of the mesenchymal tissue and a reaction of the apical rim of the syncytiotrophoblast. Following pre-treatment of the tissue with trypsin, preparations O and A′ revealed staining within the cytoplasm of the syncytiotrophoblast only, whereas preparation A also produced strong staining reaction with connective tissue and the fetal vessels.

Fig. 5. Immunohistochemical examination of the control IgG fraction on paraformaldehyde fixed placental tissue without (a) and with (b) tryptic pre-treatment. No reaction products are seen ×400.

Although examination of the decidualized endometrium using preparations O and A′ revealed no staining, a reaction was observed using preparation A (Fig. 4). This reaction, however, was less pronounced in the typical decidual cells compared with the surrounding tissue, and was apparently unaffected by trypsin treatment of the tissue.

The control preparation (C) did not stain any of the tissues which had or had not been subjected to proteolytic pre-treatment (Fig. 5).

Circulating PAPP-A (>3 m-i.u./l) was consistently detected within 28 days after conception by RIA regardless of which of the two antibody preparations (O and D) was used, and identical results were obtained (Fig. 6). After the initial detection, PAPP-A concentrations rose exponentially with a doubling time of 4·9 days until 8 weeks gestation and 10·2 days thereafter. Circulating PAPP-A was not detected in any of the

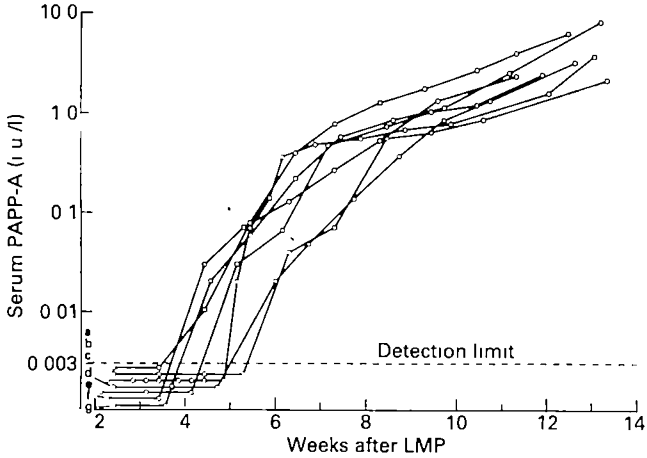

Fig. 6. Serum levels of PAPP-A during early normal pregnancy after AID (described in text)

samples obtained from the women who did not conceive or before 18 days after conception.

Discussion

The present study was undertaken to find an explanation for some of the discrepancies which have arisen from studies on tissue localization of PAPP-A, and the presence or absence of circulating PAPP-A in the non-pregnant state. Using immunoelectrophoretic techniques, we have clearly demonstrated that the Aberdeen anti-PAPP-A antiserum (Bischof *et al.* 1979) which has been extensively used in reports on tissue localization (DuBerg *et al.* 1982; Bischof *et al.* 1984*a*; Schindler & Bischof 1984; Schindler *et al.* 1984) is oligospecific. This antiserum has specificities against pregnancy zone protein, α_2-macroglobulin, β-lipoprotein and at least three additional proteins, not yet identified, which implies that whenever this antiserum has been used in localization studies, the results are to be considered inconclusive and interpreted with extreme caution. At least six proteins unrelated to PAPP-A may well have been responsible for the staining reactions seen in these studies, so that in the crude state this antiserum is unsuitable for studies on the biology of PAPP-A which involve most immunochemical techniques for measurements and localization (Bischof *et al.* 1982*a*, *b*, 1983*b*, 1984*a*, *b*).

In contrast to the crude Aberdeen anti-PAPP-A antiserum, the anti-PAPP-A IgG fractions prepared in Odense and by Dakopatts seemed to be monospecific as did the IgG fraction isolated from the Aberdeen antiserum after the additional absorption procedures. Using the monospecific IgG fractions which had been further absorbed with fetal connective tissue (O and A′), PAPP-A was found exclusively in the cytoplasm of the syncytiotrophoblast and only after tryptic pre-treatment of the formaldehyde-fixed tissue.

The localization of PAPP-A in the apical rim of the syncytiotrophoblast as reported by Wahlström *et al.* (1981) could only be reproduced using preparations which had not been absorbed with connective tissue (A and D) and only when the fixed tissue had not been pre-treated with trypsin. These data suggest that PAPP-A shares epitopes with molecular structures present in connective tissue and on the surfaces of the trophoblast as these epitopes apparently can be absorbed with PAPP-A (Wahlström *et al.* 1981) as well as with the connective tissue as demonstrated in the present report.

Our observations on the absence of circulating PAPP-A using antibody preparations O or D in a RIA for this molecule suggest that the appearance of PAPP-A in the circulation is specific for pregnancy.

Our findings here on the polyspecific nature of the anti-PAPP-A antibodies used in Aberdeen and Geneva, and the curious use of anti-PAPP-A immunoreactive fragments (instead of the whole molecule) as radiolabelled tracer (Bischof *et al.* 1981), further strengthen this view. As the specificity of competitive assays such as RIA is dependent on the characteristics of the tracer as well as the antibody, only antibody preparations with optimal specificity features i.e. O and D were used in our RIA studies. We have confirmed that the appearance of circulating PAPP-A is delayed at least 2 weeks after conception, which makes PAPP-A detection unsuitable as a biochemical test for pregnancy. The subsequent rise in serum concentrations is not as rapid as that for human chorionic gonadotrophin (hCG) or Schwangerschaftsprotein 1 (SP1) which suggests that the factors which influence the synthesis and secretion of these substances are largely independent of each other. Since depressed levels of PAPP-A are seen in imminent abortion where the fetus is still alive, and in ectopic gestation, it is possible that PAPP-A synthesis may be regulated by factors derived from within the uterus, but unrelated to the fetus (Grudzinskas *et al.* 1986).

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The content and immunohistochemical localization of placental protein 10 (PP10) in the fallopian tube

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Summary. Radioimmunoassay, gel filtration and immunoperoxidase staining were used to study the content and localization of placental protein 10 (PP10) in 15 fallopian tubes removed on medical grounds from patients aged between 35 and 53 years. PP10 was consistently present in all parts of the tube at all ages and in all phases of the menstrual cycle. The PP10 concentration in tissue ranged from 0·08 to 2·95 μg/g of tubal cytosol protein. Immunoperoxidase staining localized PP10 in monocytic and lymphoid cells that were unevenly scattered in the subepithelial layer of the mucosa. In gel filtration, PP10 from the fallopian tube and purified placental PP10 eluted in the same volume, and graded amounts of PP10-immunoreactive material from the tube and purified PP10 gave parallel dose-response curves in radioimmunoassay. We conclude that PP10 is another 'placental protein' that has been identified in the fallopian tube.

Placental protein 10 (PP10) is one of the recently discovered proteins isolated from extracts of the human term placenta. PP10 is a glycoprotein with an α_1-electrophoretic mobility containing 6·65% carbohydrate and having a molecular weight of 48 000 (ultracentrifugation) or 65 000 (SDS-PAGE) (Bohn & Kraus 1979).

Many of the so-called placental proteins are not strictly pregnancy-specific. They can be detected in seminal plasma (Ranta *et al.* 1975; Julkunen *et al.* 1985), secretory endometrium (Rutanen *et al.* 1984; Sjöberg *et al.* 1984*a*) and follicular fluid (Seppälä *et al.* 1984*a*, *b*; Sjöberg *et al.* 1984*b*). By immunoperoxidase staining PP10 has been localized in the placenta, decidua, amnion, chorion (Inaba *et al.* 1980) and secretory endometrium (Wahlstöm *et al.* 1982). We report here the occurrence of PP10 in the fallopian tube.

Materials and methods

Tissue extracts

Fallopian tubes were collected from 15 women aged 35–53 years who underwent hysterectomy and salpingectomy for the following reasons: uterine fibroids in eight, adenomyosis in four, dysmenorrhoea in two and carcinoma-in-situ of the cervix in one. Serum samples from the same patients were obtained before surgery and stored at −20°C until tested. After surgery and after routine specimens had been taken for histopathological examinations, the fallopian tubes were divided into isthmic, ampullar and fimbrial parts. The tissues were frozen and stored in liquid nitrogen. Before testing the tissues were thawed and homogenized in cold phosphate-buffered saline (PBS, pH 7·4, 4°C) containing

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Table 1. The content of PP10 in 15 fallopian tubes (μg/g cytosol protein)

Region of tube	PP10 (μg/g cytosol protein)	
	Range	Mean (SE)
Isthmic	0·12–2 40	0·50 (0·19)
Ampullar	0·08–2·95	0·64 (0·24)
Fimbrial	0·08–0·91	0·31 (0·06)

phenyl-methan-sulfonyl-fluoride (PMSF, 175 μg/ml, Merk, Darmstadt, FRG) as proteinase inhibitor. The homogenates were centrifuged at 8000 *g* for 10 min at 4°C, and the supernatants were stored at −20°C until tested by radioimmunoassay (RIA). Protein content of the supernatants was determined as described by Lowry *et al.* (1951).

PP10 radioimmunoassay

The PP10 radioimmunoassay (RIA) was performed as described previously (Tiitinen *et al.* 1985). Purified PP10 (Lot 210/236) and anti-PP10 antiserum (Lot 377ZB) were from Behringwerke AG, Marburg, FRG. Sensitivity of the assay was 2 μg/l. No cross reaction was observed with placental proteins PP5, PP12, and PP14 (Behringwerke). Tissue extract was assayed in serial doubling dilutions in PBS in order to study parallelism of dose-response curves. Statistical analysis was performed by the Mann–Whitney *U*-test.

Gel filtration

A 1×64 cm Sephacryl S-200 column (Pharmacia, Uppsala, Sweden) was used for gel filtration. Ammonium bicarbonate (0.1 M) buffer was used at a flow rate of 10 ml/h and 1·2-ml fractions were collected. The elution pattern of tubal PP10-like immunoreactivity was compared with that of purified radioactive PP10.

Immunohistochemistry

Specimens from the same fallopian tubes as used for preparation of tissue extracts were examined immunohistochemically Tissue samples were fixed in buffered formalin and embedded in paraffin before immunoperoxidase staining which was carried out as described by Wahlstrom & Seppala (1984). Anti-PP10 antiserum was used at a 1/100 dilution. Staging of the menstrual cycle was determined by histological examination of the endometrium using the criteria described by Noyes *et al.* (1950).

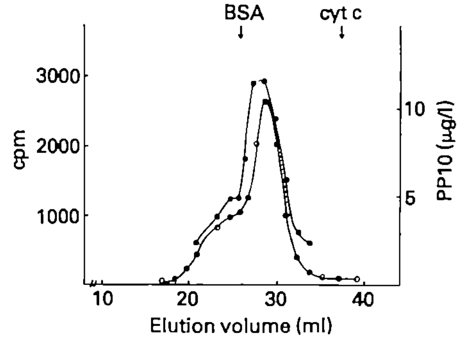

Fig. 1. Elution patterns on Sephacryl S-200 column of tubal and purified PP10: cyt c, cytochrome c (MW 12 400); BSA, bovine serum albumin (MW 67 000), (○–○) purified radiolabelled PP10; (●–●) tubal extract

Results

By RIA PP10 was detected in saline extracts from all parts of all fallopian tubes irrespective of the age of the patient, but not in any of the matched serum samples. Tissue concentration of PP10, expressed as μg/g of cytosol protein, ranged from 0·08 to 2·95 μg/g tubal protein. No difference was found in the PP10 content between isthmic, ampullar and fimbrial parts (Table 1). The tubal concentration of PP10 was independent of the phase of endometrium.

In gel filtration, PP10 of tubal extract eluted in the same volume as purified PP10 (Fig. 1). Serial dilutions of tubal homogenate and the PP10

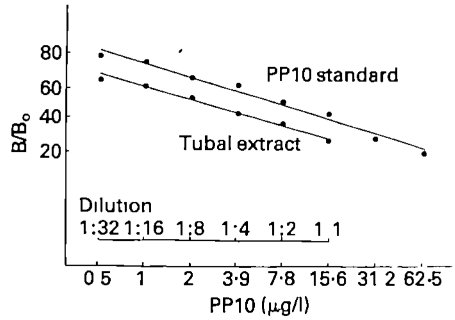

Fig. 2. Dose-response curves of purified and tubal PP10.

standard gave parallel dose-response curves (Fig. 2).

Immunohistochemically, PP10 was demonstrated in four out of 15 fallopian tubes. No staining of mucosal epithelium was seen, but underneath the epithelium there were accumulations of monocytic and lymphoid cells which sometimes took the positive stain. Moreover, tubal secretion contained amorphous material which stained positively (Fig. 3).

Discussion

In the present study a protein originally designated as 'placental' was found in the fallopian tube. This was not surprising, since PP10 has been found in the human secretory endometrium (Wahlström *et al.* 1982), and both tissues derive from the same embryonic origin, the Müllerian duct. Moreover, PP10 is not the only pregnancy protein that has been found in the tubal and uterine mucosa. Pregnancy-associated plasma-protein-A (Sjöberg *et al.* 1986) and PP14 (Julkunen *et al.* 1986) have likewise been detected in the tubal mucosa, and the presence of these proteins in both the endometrium and the tube appears to be the rule.

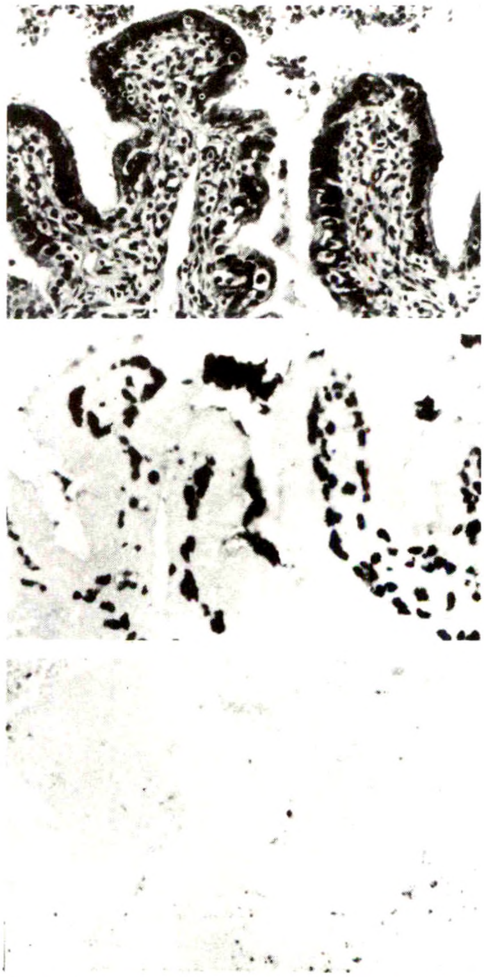

Fig. 3. PP10 in fallopian tube. Top, haematoxylin and eosin; middle, anti-PP10 antiserum; bottom, anti-PP10 absorbed with purified PP10; 1:300.

The localization of PP10 in the tubal mucosa is different from any other pregnancy protein. The other 'placental' proteins, PAPP-A and PP14, are localized in the ciliated epithelial cells, whereas PP10 occupies a quite different position in the subepithelial layer of the mucosa. Although PP10 appeared in the monocytic and lymphoid cells, these fallopian tubes did not show any histological evidence of inflammatory reaction. Matched serum samples were PP10 negative at the detection level of 2 μg/l, and so were the buffy coat cells from normal human blood when studied by RIA.

The significance of our finding of PP10 in the fallopian tube awaits clarification of the protein's function.

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The relation between aldosterone concentrations in plasma and saliva during pregnancy

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Summary. The concentrations of aldosterone and glucocorticoids (cortisol+cortisone) were measured in saliva and plasma samples obtained from healthy women during early (11–19 weeks), mid (24–29 weeks) and late (32–37 weeks) pregnancy. There was a progressive increase in mean aldosterone levels in both saliva and plasma throughout pregnancy, though at each stage of pregnancy the range was very wide. Glucocorticoid levels increased up to mid-pregnancy and then remained constant. At no stage were aldosterone and glucocorticoid levels significantly correlated. The proportion of free (non-protein bound) aldosterone in plasma, and the saliva:plasma ratio of aldosterone did not differ from the non-pregnant range at any stage of pregnancy. We conclude that measurement of aldosterone concentration in saliva is a convenient and valid method for the estimation of plasma free aldosterone in pregnancy and so provide a non-invasive technique for assessing aldosterone status throughout pregnancy.

During pregnancy increases have been reported in the rate of excretion of aldosterone in the urine (Martin & Mills 1956), the rate of secretion of aldosterone (Jones *et al.* 1959), and the plasma concentration of aldosterone (Weir *et al.* 1975; Smeaton *et al.* 1977; Dux *et al.* 1984; Karlberg *et al.* 1984). Furthermore, Tait *et al.* (1962) have found the metabolic clearance rate of aldosterone to be similar in pregnant and non-pregnant subjects. The mechanism by which the secretion rate and plasma concentration of aldosterone are raised during pregnancy is not known. Mean values for plasma renin activity (PRA) and angiotensin-II (A-II) concentration are raised during pregnancy but the normal relation between these factors and aldosterone level is disturbed (Weir *et al.* 1975). Paradoxically it has been found that hypertension during pregnancy is often associated with relatively low aldosterone levels (Weir *et al.* 1973).

Elucidation of the role of aldosterone during pregnancy would be facilitated by a simple and non-invasive technique for the assessment of aldosterone status; measurement of saliva aldosterone concentration would fulfill this requirement. It has been shown in non-pregnant subjects that levels of saliva aldosterone correlate well with plasma aldosterone concentrations (PA) (McVie *et al.* 1979; Few *et al.* 1984) and is sensitive to changes in the latter (Few *et al.* 1984). Moreover, saliva aldosterone concentration approximates to the concentration of free (non-protein bound) aldosterone in plasma (Few *et al.* 1986) which is generally believed to be the physiologically active fraction.

In non-pregnant subjects albumin is the principal protein in plasma which binds aldosterone but as the concentration of corticosteroid binding globulin increases with advancing pregnancy, this becomes the principal aldosterone binding protein (Dunn *et al.* 1981). Although it

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Table 1. Comparison of the concentrations of aldosterone and glucocorticoids in saliva and plasma during pregnancy and in non-pregnant subjects

		Stage of gestation		
	Non-pregnant	Early	Mid	Late
Weeks of gestation (mean (SD))	—	13·9 (3·0)	26·2 (1·4)	35 (2)
Number of subjects	18	15	19	18
(1) Plasma aldosterone (pmol/l)				
Mean	363	770	1295	1870
Range	120–935	260–2470	575–2580	585–3980
(2) Saliva aldosterone (pmol/l)				
Mean	68	132	274	420
Range	29–118	45–495	100–612	112–758
(3) Plasma glucocorticoid (nmol/l)				
Mean		525	920	860
Range		320–790	470–1200	390–1400
(4) Saliva glucocorticoid (nmol/l)				
Mean		21·5	31	31
Range		15–32	18–65	16–42
(5) Plasma % free aldosterone				
Mean (SD)	30·3 (3·85)	28·4 (1·37)	28·3 (2·51)	29 (2·9)
(6) Plasma free aldosterone (pmol/l)				
Mean	113	219	366	541
Range	40–280	70–440	150–775	170–755
(7) 2:6 mean (SD)	0·63 (0·23)	0·56 (0·033)	0·75 (0·031)	0·78 (0·044)
Correlations				
1 *vs* 2	0·43	0·91**	0·86**	0·85**
1 *vs* 3		0·27	0·27	0·32
3 *vs* 4		0·52*	0·55*	0·23
2 *vs* 4		0·19	0·22	0·004
2 *vs* 6	0·43	0·83**	0·92**	0·88**

* $P<0{\cdot}05$; ** $P<0{\cdot}001$.

was calculated that the proportion of free aldosterone would not be affected by this change (Dunn *et al.* 1981), nevertheless it seemed possible that it might in some way influence the transfer of aldosterone from the plasma to the saliva. We have therefore examined the relation between saliva and plasma aldosterone concentrations during pregnancy in order to establish to what extent assay of its concentration in saliva is a useful index of aldosterone status in pregnancy.

Subjects and methods

Plasma was obtained from the blood samples drawn routinely from women at the initial, and 26 and 36 week visits to the antenatal clinic. Saliva was collected simultaneously into plastic tubes and was frozen, thawed and centrifuged before assay. All the women were healthy and none had a blood pressure exceeding 140/90 mmHg. None contributed more than one set of samples to the study.

The antibody used for the radioimmunoassay (RIA) of glucocorticoids was obtained by immunizing rabbits against cortisol-3-CMO conjugated to bovine serum albumin (BSA). [1,2,6,7-^{3}H]cortisol was purchased from Amersham International (Aylesbury, UK). All other reagents were as described previously (Few *et al.* 1984). The methods for the estimation of plasma and saliva aldosterone concentrations and the binding of aldosterone by plasma proteins have been described in detail elsewhere (Few *et al.* 1984, 1986).

Glucocorticoid determination

Plasma was diluted 1:10 in pH 7·4 phosphate buffer and heated in a water bath at 60°C for 30

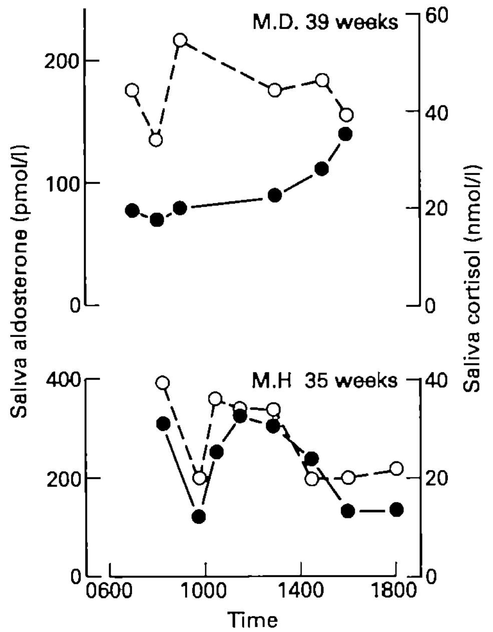

Fig. 1. Diurnal saliva aldosterone (- - -) and glucocorticoid (———) levels in two hypertensive, third trimester patients

min to inactivate corticosteroid binding globulin. Aliquots (50 µl) of this inactivated plasma, of saliva or of cortisol standards (30–2000 pg/50 µl) were mixed with 500 µl of a RIA reagent consisting of a 1:8000 dilution of the antibody in 0·1% BSA in pH 7·4 phosphate buffer to which 1 µCi [^{3}H]cortisol was added per 80 ml. The assay tubes were allowed to stand overnight at 6°C and free and bound fractions were separated using dextran-charcoal exactly as in the aldosterone assay. Tritium was assayed in the supernatant (bound) fraction by liquid scintillation counting.

Extracting and chromatography of saliva for the assessment of specificity was carried out as described previously (Few *et al.* 1984).

Results

Heat inactivated, diluted plasma, and saliva, collected from late pregnancy subjects, were extracted with dichlormethane which removed all the immunoassayable aldosterone and glucocorticoids. When these extracts were submitted to thin-layer chromatography (TLC) all the immunoassayable aldosterone from plasma and saliva had the same mobility as authentic aldosterone. Immunoassayable glucocorticoid from plasma was predominantly (>80%) accounted for by cortisol, but in the case of saliva a substantial proportion (>50%) was due to cortisone and a small proportion had the same mobility as 11-deoxycortisol. When we compared the direct assay for glucocorticoid in saliva (x) with the specific assay of cortisol, which was isolated by TLC (y), they were found to be related by the expression $y = 0{\cdot}35x - 0{\cdot}384$ ($r = 0{\cdot}97$; $P < 0{\cdot}001$; $n = 10$).

When varying volumes of pooled, late pregnancy saliva were assayed for either aldosterone or glucocorticoids, in both cases the quantity of steroid was proportional to the volume of saliva assayed.

The principal findings with respect to pregnancy are summarized in Table 1. Standard deviations of the concentrations of aldosterone and glucocorticoids are not given because of the very wide range of values which are probably not normally distributed. In the early pregnancy group saliva aldosterone concentration was greater than 150 pmol/l in four subjects and less than 100 pmol/l in seven subjects. In this group the duration of pregnancy ranged from 11 to 19 weeks but this did not correlate with the concentration of aldosterone in either saliva or plasma.

Figure 1 shows the diurnal changes in saliva aldosterone and glucocorticoid levels in two women admitted to hospital on account of hypertension. In both cases aldosterone level fluctuated considerably.

Discussion

During pregnancy, particularly the third trimester, steroid production is markedly greater than in the non-pregnant condition. It therefore seemed prudent to re-examine the specificity of the saliva and plasma aldosterone assays in this context; the very high values that we have found for aldosterone appear to be a true indication of concentration as no cross reacting compounds could be detected. The situation is more complex with the glucocorticoids as our cortisol antibody strongly cross reacts with other 17 α-hydroxycorticosteroids such as cortisone and 11-deoxycortisol. This lack of specificity is offset by the fact that there is substantial oxidation of cortisol to cortisone during transit through the salivary glands (Brooks & Brooks 1984) and even the circulating cortisone derives from cortisol by extra-adrenal oxidation. There would therefore appear to be no serious disadvantage to measuring the aggregate of cortisol and cortisone as an index of adrenocortical activity. This explains why our saliva glucocortisoid levels are substantially higher than some values reported earlier for saliva cortisol in late pregnancy (Bustamente & Crabbé 1984).

Our data on concentrations of aldosterone in saliva and plasma, and the protein binding of aldosterone in plasma, confirm and extend the findings of earlier investigators. Of particular importance was the finding that even when aldosterone levels were grossly elevated (as in the third trimester of pregnancy) the relation between saliva and plasma concentrations of aldosterone that we had previously found in non-pregnant subjects was maintained. We are therefore confident that even in pregnancy, with its unique hormonal milieu, the direct assay of aldosterone in saliva offers a simple and reliable method of estimating plasma free aldosterone level and hence of assessing aldosterone status by a non-invasive technique.

Early investigators utilized urine collections for the determination of the rates of excretion and secretion of aldosterone. Such techniques gave a value averaged over the period of collection. With the development of RIA the measurement of plasma aldosterone has become the preferred technique for assessing aldosterone status, but aldosterone has a high metabolic clearance (~1 l/min) and this can lead to rapid fluctuations in the plasma concentration. Consequently, a single blood sample is not necessarily a good index of aldosterone status in the longer term. While measurement of saliva aldosterone also has the same temporal limitations, it is much easier to collect a series of saliva than of blood samples. Moreover, the direct assay permits handling of large numbers of saliva samples in the laboratory. It is thus relatively easy to construct an aldosterone profile based upon saliva sampling and the direct assay of aldosterone This is illustrated in Fig. 1 which shows that in two hypertensive women in later pregnancy aldosterone, and cortisol, levels fluctuated considerably over a period of a few hours.

In conclusion we recommend the determination of aldosterone concentration in series of saliva samples as a useful technique in the elucidation of the role of elevated aldosterone production during pregnancy.

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The use of a calcium antagonist (nifedipine) to suppress preterm labour

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Summary. The efficacy of an orally administered calcium antagonist, nifedipine, in suppressing premature uterine activity, was compared with intravenous ritodrine and no treatment. Nifedipine was found to be significantly more effective than ritodrine or withholding therapy, and was almost devoid of side-effects.

Over the past decade there have been remarkable advances in the management of preterm infants, but the sequelae of preterm labour are still responsible for a significant amount of perinatal morbidity and mortality, particularly in those infants under 28–30 weeks gestation. There is still a place for attempting to suppress premature uterine activity, especially in units without ready access to neonatal intensive care facilities.

The mainstay of current treatment is an intravenous infusion of a β-sympathomimetic agent, which may be followed by oral maintenance therapy. The incidence of troublesome side-effects and the debatable efficacy of these agents prompts the search for better drugs.

Activity in uterine muscle, *in vitro,* is dependent upon extracellular calcium (Bolton 1979), so that it would be anticipated that contraction would be inhibited by calcium antagonists.

In recent years the effects of the calcium antagonist, nifedipine, have been studied on non-pregnant uterine muscle (Ulmsten *et al.* 1978; Formann *et al.* 1979), postpartum uteri primed with oxytocin or prostaglandin $F_{2\alpha}$ (Formann *et al.* 1982), in early pregnancy (Andersson *et al.* 1979) and in preterm labour (Ulmsten *et al.* 1980).

This study compares the effects of a calcium antagonist (nifedipine) with those of a conventional β-sympathomimetic drug (ritodrine) and with no treatment in a control group. There were 20 women in each group.

Patients and methods

One problem which has made it difficult to assess studies on the suppression of preterm labour is that of making the diagnosis, particularly in those women who have no evidence of cervical dilatation on admission. There is no doubt that a substantial proportion of these women are not really in preterm labour and would not give birth if left alone. However, there is no way of deciding which women with apparent uterine contractions and little or no cervical dilatation will proceed and which will not. Also, in the belief that the earlier treatment is commenced, the more successful it is likely to be, they all tend to be treated which leads to the high placebo response found in most studies.

In order to minimize the possible influence of other factors and particularly to enable better matching of the three groups for fairer comparison, strict criteria were laid down for inclusion in the trial. Women were considered suitable for inclusion if they had singleton pregnancies with intact membranes between 20 and 35 weeks gestation and were contracting at least

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once every 10 min. Women were not suitable for inclusion in this study if they had a multiple pregnancy, polyhydramnios, ruptured membranes, a history of cervical surgery, a history of mid-trimester abortion or previous preterm delivery, a history of any medical condition which would contraindicate the use of either of the drugs, if there was any evidence of intra-uterine infection or any irregularity of the fetal heart, where there was a history of antepartum haemorrhage or if the cervix was >4 cm dilated.

For the purpose of this study only one course of treatment was given. If contractions recurred a few days after completion of the course of treatment, the case was discussed with the appropriate consultant as to whether further treatment was to be given. In this series no additional treatment was considered necessary. Thus the 'postponement of delivery' interval is a valid measure of the treatment regimen selected.

It is accepted that many of these exclusions would normally be acceptable indications for attempting to suppress uterine activity. We deliberately excluded them as the study groups are relatively small and inclusion of these patients would render the groups less comparable. A double-blind placebo type of trial was not possible here, as the ethics committees involved would not agree to the use of placebos and the different route of administration for the two drugs precluded a double-blind study.

Patients who were potentially suitable for inclusion were interviewed and their written informed consent obtained before being randomly allocated to either active treatment group. Women under the care of consultants whose policy was not to suppress preterm labour were used for the no treatment control group.

In each group there was an initial 30 min observation period during which time the fetal heart and uterine activity were assessed After this time the appropriate treatment was commenced.

Treatment was deemed successful if contractions were abolished and no further cervical dilatation occurred during treatment and there was no recurrence of contractions within 48 h of stopping treatment.

Ritodrine

An intravenous infusion was established beginning at 50 μg/min rising by 50 μg increments every 10 min to a maximum of 300 μg/min or until contractions ceased; or there was a maternal tachycardia of 140 beats/min; or a fetal tachycardia of 180 beats/min; or other side-effects were intolerable.

The effective dose was maintained for 12 h after which the dose was gradually reduced unless contractions recurred. When there had been no contractions for 12 h the infusion was discontinued and 10 mg of ritodrine was given orally at 4-h intervals for 48 h

Nifedipine

An initial dose of 30 mg was given orally, followed by 20 mg at 8-h intervals for 3 days.

Early experience elsewhere suggested there might be a delay of up to 1 h before the effects of the nifedipine became apparent. Therefore, a total of 2 h was allowed (including the initial observation period) before reassessment. If the contractions were undiminished, as observed on the cardiotocograph, the treatment was deemed to have failed and intravenous ritodrine was given (as the standard treatment for the unit), at the request of the ethics committee.

For both groups the maternal pulse and blood pressure were recorded every 15 min for the first 2 h and then hourly for 24 h.

Results

There were no significant differences between the three groups for age, weight, parity or length of gestation (Table 1).

Table 2 shows that nifedipine was considerably more successful in halting labour than either ritodrine or no treatment. Chi-squared analysis found no statistically significant difference between the control group and the ritodrine treated group, but there was a significant difference ($P<0 \cdot 05$) between the nifedipine treated group and both the control group and the ritodrine-treated group.

Effects on cardiovascular system

Although nifedipine caused a reduction in both systolic and diastolic blood pressure, the difference was not statistically significant. Both ritodrine and nifedipine caused a similar significant rise in the fetal heart rate but only ritodrine caused a significant rise in maternal heart rate.

Table 3 shows that, statistically, nifedipine caused a significantly greater postponement of

Table 1. Clinical details of the three study groups

Clinical details	No treatment (n = 20)	Ritodrine (n = 20)	Nifedipine (n = 20)
Age (years)	24 9 (4·4)	24·6 (3·6)	23·5 (3 9)
Gestation at treatment (weeks)	32 9 (1 7)	31·9 (1·6)	32 3 (1·4)
Maternal weight (kg)	63 9 (7 6)	67·1 (9·3)	62 5 (8·1)
Primigravidae (n)	3	4	2
Nulliparae (n)	6	6	5

Results are mean (SD).

Table 2. Results of treatment in the three study groups

Result	No treatment (n = 20)	Ritodrine (n = 20)	Nifedipine (n = 20)
Success	7	9	15
Failure	13	11	5*

* Only one of these five patients responded to ritodrine after nifedipine failed to suppress uterine activity

delivery compared with ritodrine or no treatment, and resulted in babies of greater birthweight. Apgar scores were similar in the three groups and there were no stillbirths nor perinatal deaths.

Significant side-effects

Troublesome side-effects were common with ritodrine therapy, and 13 women complained of palpitations and feelings of anxiety In women receiving nifedipine, some 90% experienced flushing, mainly of the face, neck and chest but this was troublesome in only one woman, and one other woman experienced marked nausea. Women who received no tocolytic agent did not complain of any real symptoms, although some 'side-effects' have been noted in previous studies where placebos were used.

Discussion

Over the past 15 years a number of drugs have been used to suppress uterine activity, either alone or in combination. Intravenous ethanol has fallen into disuse as it caused troublesome nausea, vomiting and hangovers and it was less effective than β-sympathomimetic agents (Lauerson *et al.* 1977). Many β-sympathomimetic drugs have been tried, with claims that the more recently introduced agents were more uterospecific with fewer systemic side-effects

Ritodrine appears to be the most widely used drug at the present time. Taken orally as a prophylactic measure in women thought to be at increased risk of preterm labour, it has not proved effective (Walters & Wood 1977; O'Connor *et al.* 1979). Used intravenously for the suppression of established uterine activity there are conflicting reports of its efficacy (Merkatz *et al.*

Table 3. Outcome of pregnancy in the three treatment groups

	No treatment (n = 20)	Ritodrine (n = 20)	Nifedipine (n = 20)
Time from presentation to delivery (days)	19·3 (6·1)	25·1 (5 7)	36·3 (5·1)*
Birthweight (g)	2860 (258)	3020 (326)	3225 (432)

Results are mean (SD) values

* Significantly longer compared with other two groups ($P<0·001$) The group includes five women treated with intravenous ritodrine after nifedipine failed (trial protocol), labour was suppressed in only one and delivery delayed for 17 days

1980; Hemminki & Starfield 1978; Spellacy *et al.* 1979). The conclusion reached by reviewers of published studies is that any therapeutic advantage is small and the wholesale use of these agents cannot be justified on present evidence (Hemminki & Starfield 1978; Spellacy *et al.* 1979), particularly in view of the high incidence of side-effects. In addition this group of drugs is not suitable for women with significant cardiovascular disease or diabetes.

As with the β-sympathomimetic drugs, the cardiovascular effects of calcium antagonists could theoretically be a limiting factor in their use (Nayler & Horowitz 1983). It has been found that nifedipine exhibits greater selectivity for inhibition of uterine activity relative to its cardiovascular effects (Granger *et al.* 1985). The effects on systolic and diastolic blood pressure have been studied before. For ritodrine the effects appear to be variable, the mean falling in some studies (Spellacy *et al.* 1979) and rising in others (Lauerson *et al.* 1977) and being unchanged in others. The studies on nifedipine have not shown a significant change but suggest there may be transient cardiovascular effects for up to 2 h (Ulmsten *et al.* 1980).

The well-recognized tachycardia caused by β-sympathomimetic agents was seen. Although there is no sustained tachycardia with nifedipine there appears to be a transient maternal effect as reported by Ulmsten *et al.* (1980) and, in our study, also on the fetus which has not been reported before.

In previous studies with β-sympathomimetic agents, the postponement of delivery has shown a marked variation with an average comparable to our findings. In the series reported by Ulmsten *et al.* (1980) nifedipine effected a delay of only 14 days, but the initial observation period before treatment was 5 h and this would permit better selection of those women in true preterm labour by excluding many with 'non-specific' uterine contractions which resolve of their own accord. Based on the view that the sooner treatment is commenced the more effective it will be, neither we nor the ethics committee thought it justifiable to wait for this length of time before starting treatment.

We accept that the trial design is open to criticism but within the constraints mentioned above we believe this study allows a fair comparison of the three groups with the inclusion of the no treatment control group and each patient acting as their own control in so far as the cardiotocograph showed whether there was any alteration in uterine activity related to treatment.

The study shows that nifedipine was significantly more effective than ritodrine or no treatment and was almost devoid of significant side-effects. It may, therefore, be the most appropriate agent for short-term use in diabetics. This study did show a definite lag time before the nifedipine started to work, this may be reduced by asking the patient to crush the capsule and absorb the contents sublingually.

Because of the relatively small numbers involved caution must be exercised in the interpretation of the results, but we believe that further study is warranted, preferably as a coordinated multicentre trial.

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Does 24-hour supervisory staff coverage in the labour and delivery area change the emergency caesarean section rate?

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Summary. The influence on the emergency caesarean section rate of 24-h supervisory staff coverage in the labour and delivery area was investigated. In period I (1978–1979), the supervisory staff were inside the hospital from 07.01 to 17.00 hours, and on call at home from 17.01 to 07.00 hours of the next day, and in period II (1980–1981), the supervisory staff were inside the hospital 24 h a day. The section rate for fetal distress increased during period II. The rate for maternal complications also increased in the 17.01–24.00 hours shift and decreased in the 07.01–17.00 hours shift during period II. However, the overall emergency caesarean section rate did not change between the two periods.

A steadily increasing caesarean section rate has characterized obstetric practice and has been the cause of concern to the profession and to the general public (Petitti *et al.* 1979; Zdeb *et al.* 1980; Ingemarsson *et al.* 1981; Hall & Alexander 1982). This increase in the section rate is thought to be due to the relative safety of the operation for the woman; extension of the indications for caesarean section and the use of fetal heart rate monitoring (Minkoff & Schwarz 1980). The possible contribution of organizational changes within the hospital setting has received minimal consideration. Differences in attitude between obstetricians may have influence in the decision to perform caesarean section. The present study was conducted to determine whether 24-h supervisory staff coverage in the labour and delivery area changed the emergency caesarean section rate.

Patients and methods

A retrospective analysis of emergency caesarean sections was made during two periods between 1978 and 1981 at Henry Ford Hospital, Detroit, Michigan. At all times, the labour and delivery area was staffed by resident obstetricians for 24 h a day, 7 days a week under the direction of supervisory staff obstetricians (board-certified or board-eligible obstetricians and gynecologists). Since 1980, the supervisory staff obstetricians have remained in the labour and delivery area at all times to supervise the residents. Before 1980, the supervisory staff obstetricians were in the labour and delivery area from 07.01 to 17.00 hours were on call at home from 17.01 to 07.00 hours of the next day from Monday to Friday and on Saturday and Sunday, they were on call at home 24 h a day. Only the emergency caesarean sections were included in the study. The indications for operation were classified as: dystocia, malpresentations, fetal distress, uterine bleeding (including placental abruption and placental praevia), maternal complications

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Table 1. Comparison of patients and obstetricians between two periods

	Period I (1978–1979)		Period II (1980–1981)	
Characteristic	No	(%)	No.	(%)
Number of patients	312	(100)	528	(100)
Age (years)				
≤17	34	(10·9)	64	(12·1)
18–35	253	(81·1)	412	(78·0)
>35	25	(8·0)	52	(9·9)
Race				
Caucasian	141	(45·2)	231	(43·8)
Black	131	(42·0)	242	(45·8)
Other	40	(12·8)	55	(10·4)
Source				
Private	208	(66·7)	364	(69·0)
Ward (Public)	104	(33·3)	164	(31·0)
Pregnancies				
1	93	(29·8)	171	(32·4)
2	97	(31·1)	150	(28·4)
3	87	(27·9)	154	(29·2)
≥4	35	(11·2)	53	(10·0)
Parity				
0	100	(32·1)	158	(29·9)
1	81	(26·0)	148	(28·0)
2	72	(23·1)	110	(20·8)
3	43	(13·7)	79	(15·0)
≥4	16	(5·1)	33	(6·3)
Abortions				
0	209	(67·0)	365	(69·1)
1	47	(15·1)	68	(12·9)
2	40	(12·8)	74	(14 0)
≥3	16	(5·1)	21	(4·0)
Number of supervisory staff obstetricians	14		20	
Year of residency completion				
Before 1960	1	(7)	2	(10)
1960–1969	3	(21)	3	(15)
1970–1975	4	(29)	5	(25)
1976–1980	6	(43)	10	(50)
Average number of resident obstetricians in labour and delivery area at any given time	1·5		2·5	

(including hypertension, diabetis mellitus and so on), prematurity-premature rupture of membrane, and other indications. The category of 'other' included cases in which indications could not be clearly defined. The distribution was analysed according to the time of the day (00.00–07.00 hours, 07.01–17.00 hours, 17.01–24.00 hours). Finally the supervisory staff was divided into four groups, according to the year in which they completed residency training to investigate whether the indications for caesarean section varied between the groups.

Statistical analysis was performed with the χ^2 test, and the level of significance was selected as $P<0{\cdot}05$.

Results

The characteristics of the patients were identical in the two periods, although the number of sec-

Table 2. Relation between study periods and indications for emergency caesarean section

Deliveries	Period I (1978–1979)		Period II (1980–1981)	
	No.	(%)	No.	(%)
Total deliveries	3619	(100)	5782	(100)
Emergency caesarean section	312	(8·6)	528	(9·1)
Dystocia	139	(3·8)	215	(3·7)
Malpresentation	69	(1·9)	121	(2·1)
Fetal distress*	24	(0·7)	64	(1·1)
Uterine bleeding	20	(0·5)	36	(0·6)
Maternal complications	40	(1·1)	71	(1·2)
Prematurity and PROM	13	(0·4)	17	(0·3)
Others	7	(0·2)	4	(0·1)

*$P = 0{\cdot}038$ (χ^2 test)

PROM, Premature rupture of membranes

tions increased from 312 in period I (1978–1979) to 528 in period II (1980–1981). There were six more supervisory staff in period II, one was in the Befor 1960 group, one in the 1970–1975 group and four in the 1976–1980 group (Table 1). The emergency caesarean section rate did not change significantly between the two periods (8·6% in period I compared with 9·1% in period II). A change in the distribution of indications for section was observed in that the percentage done for fetal distress increased from 0·7% in period I to 1·1% in period II ($P = 0{\cdot}038$). The percentages for all other indications remained essentially the same (Table 2).

Changes in distribution by time of day were observed for sections done for maternal complications. About equal percentages were performed in the 00.00–07.00 hour shift, but in period II, an increase in the 17.01–24.00 hours shift (15% compared with 37%) and a decrease in the 07.01–17.00 hours shift (70% compared with 49%) occurred ($P = 0{\cdot}039$). When all indications were considered, there was a 3% increase (24% to 27%) in the 00.00–07.00 hours shift, a 7% decrease (49% to 42%) in the 07.01–17.00 hours shift, and a 4% increase (27% to 31%) in the 17.01–24.00 hours shift. Overall, the net effect of 24-h supervisory staff coverage was a 7% increase in emergency caesarean sections performed between 17.00 hours and 07.00 hours (Table 3).

The year that residency training was completed had a significant influence on the rate of sections performed for maternal complications (an increase; $P < 0{\cdot}001$) and for dystocia (a decrease; $P = 0{\cdot}0014$) for the group of 1970–1975. This group had a different rate of section for maternal complications (23%) from the

Table 3. Relation between time of delivery and indication for emergency caesarean section

Indication	Shift 00.00–07.00 hours				Shift 07.01–17.00 hours				Shift 17.01–24.00 hours			
	I		II		I		II		I		II	
	No.	(%)	No	(%)	No.	(%)	No.	(%)	No.	(%)	No	(%)
Dystocia	32	(23·0)	68	(31·6)	59	(42·5)	75	(34·9)	48	(34·5)	72	(33·5)
Malpresentation	18	(26·1)	30	(24·8)	38	(55·1)	69	(57·0)	13	(18·8)	22	(18·2)
Fetal distress	9	(37·5)	22	(34·4)	7	(29·2)	22	(34·4)	8	(33·3)	20	(31·2)
Uterine bleeding	4	(20·0)	10	(27·8)	11	(55·0)	13	(36·1)	5	(25·0)	13	(36·1)
Maternal complications*	6	(15·0)	10	(14·1)	28	(70·0)	35	(49·3)	6	(15·0)	26	(36·6)
Prematurity and PROM	3	(23·1)	3	(17·7)	7	(53·8)	9	(52·9)	3	(23·1)	5	(29·4)
Others	2	(28·6)	0	(0)	4	(57·1)	1	(25·0)	1	(14·3)	3	(75·0)
All indications	74	(23·7)	143	(27·1)	154	(49·4)	224	(42·4)	84	(26·9)	161	(30·5)

Period I. Years, 1978 and 1979 Period II Years, 1980 and 1981.

*$P = 0{\cdot}039$ (χ^2 test)

PROM, Premature rupture of membranes.

Table 4. Relation between years that supervisory staff completed residency and indication for emergency caesarean section

	Completion of residency							
	Before 1960		1960–1969		1970–1975		1976–1980	
Main indications	No.	(%)	No	(%)	No.	(%)	No.	(%)
Dystocia*	33	(44·6)	68	(46·6)	73	(31·3)	180	(46·5)
Malpresentation	22	(29·7)	27	(18·5)	49	(21·0)	92	(23·8)
Fetal distress	6	(8·1)	13	(8·9)	26	(11·2)	43	(11·1)
Uterine bleeding	6	(8·1)	9	(6·2)	21	(9·0)	20	(5·2)
Maternal complications**	7	(9·5)	20	(13·7)	54	(23·2)	30	(7·7)
Prematurity and PROM	0	(0)	5	(3·4)	8	(3·4)	17	(4·4)
Others	0	(0)	4	(2·7)	2	(0·9)	5	(1·3)
Total	74	(100)	146	(100)	233	(100)	387	(100)

*$P = 0{\cdot}0014$; **$P<0{\cdot}001$ (χ^2 test).
PROM, Premature rupture of membranes.

other three groups (10%, 14% and 8%); and for dystocia (31% *vs* 45%, 47% and 47%) (Table 4).

Discussion

The possibility of obstetrician bias as a factor influencing the section rate could be studied in this institution because of a change in the on-call policy by supervisory staff. When the labour and delivery area was covered by supervisory staff for 24 h a day, 7 days a week, as in period II in this study, the patients were managed mainly by the supervisory staff with the assistance of the residents. Before 1980, patients were managed mainly by residents after 17.00 hours.

Several variables could have influenced the comparison of the two periods studied. The total number of deliveries increased from 3619 in period I to 5782 in period II, a 60% increase. The number of supervisory staff increased from 14 to 20, a 70% increase. There was also an increase in the average number of residents assigned to the labour and delivery area at any given time from 1·5 to 2·5, a 60% increase. The degree of active participation by residents in the care of private and ward patients was similar in the two periods and management policies were constant. The facilities in the labour and delivery area were similar during that 4-year period.

In period II, six more supervisory staff joined the department and four of them belonged to the 1976–1980 group (Table 1). To control this variable, comparisons were made to see if there was a relation between the distribution of indications for caesarean section and the years in which the supervisory staff had completed residency training. In the 1970–1975 group, the number of caesarean sections increased for maternal complications, but decreased for dystocia. It should be noted that a perinatologist was included in that group during both periods. Because there were more high-risk patients seen in his clinic, he might encounter more maternal complications and perform more sections for that indication. Except for this difference, there was no relation between the distribution of indications and time of completion of residency training. Since this perinatologist was present and functioning in the same way in both the study periods, this was not considered to be a contributory factor to the differences between two periods. The similarity in the patient population as well as in the obstetricians characteristics during the two periods thus permits the influence of 24-h supervisory staff coverage on the emergency caesarean section rate to be studied.

In this study the overall emergency section rate did not change significantly between the two periods. The number of caesarean sections performed for fetal distress increased with the presence of obstetricians in the labour and delivery area 24 h a day. This was probably due to the increased recognition of abnormal fetal heart rate patterns because of the constant presence of more senior personnel.

A universal preference to work during the regular working day and to preserve the usual hours for rest has been proposed a force that may influence decisions about performing caesarean sections. Phillips *et al.* (1982) did not find any difference between the percentages of deliveries on weekends and weekdays, although Poma (1982) and Goodlin (1983) found that more caesarean sections were done for dystocia at certain times of the day. In our study, significantly more sections for maternal complications were performed in the 17.01–24.00 hours shift and significantly fewer in the 07.01–17.00 hours shift, with supervisory staff in the hospital at all times. Overall, more inductions were done for medical complications with 24-h supervisory staff coverage, and then, since most inductions were performed early in the morning, failure of induction was recognized and caesarean section was performed during the 17.01–24.00 hours shift. However, the overall 7% increase in the emergency caesarean section rate between 17.00 and 07.00 hours with 24-h supervisory staff coverage was not statistically significant. Our data suggest that 24-h supervisory staff coverage in the labour and delivery area does not significantly change the emergency caesarean section rate.

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Maternal stress response associated with caesarean delivery under general and epidural anaesthesia

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Summary. The maternal stress response to caesarean delivery with either general or epidural anaesthesia was investigated. Patients given a general anaesthetic showed statistically significant increases in blood pressure, heart rate, and levels of plasma catecholamines, cortisol and glucose. Epidural anaesthesia, to at least the T_6 dermatome, obtunded these responses. The significance of these findings to the choice of method of anaesthesia is discussed.

General anaesthesia and major surgery are associated with sympathoadrenal activation leading to changes in plasma cortisol, insulin, catecholamines and glucose. Release of cortisol and catecholamines cause both biochemical changes (hyperglycaemia, lipolysis) and cardiovascular sequelae (usually tachycardia and hypertension). In the presence of hyperglycaemia the pancreatic hormone insulin does not respond in the usual physiological manner (Brandt *et al.* 1976).

While this stress response is attributable in part to general anaesthesia (Hunter 1959; Oyama *et al.* 1972), the incision and subsequent surgical manipulations are the major activators, intra-abdominal surgery being a more potent stimulus than body surface operations (Clarke 1970). Epidural and spinal anaesthesia, by blocking the afferent impulses from the operation site, prevent the rise in glucose (Brandt *et al.* 1976) and cortisol (Gordon *et al.* 1973). Pflug & Halter (1981) reported that plasma catecholamine levels are lowered during high spinal blocks during which rises in glucose and cortisol did not occur. Deep inhalational anaesthesia established before noxious surgical stimuli can, like adequate spinal anaesthesia, prevent the adrenergic and cardiovascular response seen during lighter planes of anaesthesia (Roizen *et al.* 1981). Moderate doses of fentanyl (20 μg/kg) can attenuate the hormonal and cardiovascular response to major gynaecological surgery (Blunnie *et al.* 1983) and much larger doses (60 μg/kg), given to patients undergoing heart surgery, completely block the cardiovascular and hormonal responses to tracheal intubation and sternotomy (Sebel *et al.* 1981).

General anaesthesia for caesarean section requires a rapid sequence induction to secure a safe airway and a very light level of anaesthesia between induction of anaesthesia and the birth of the infant to avoid depression of the newborn. This would be expected to cause a large ‘stress response’. This study reports a comparison of the hormonal and cardiovascular changes associated with general or epidural anaesthesia when used for elective caesarean section.

Patients and methods

Patients selected for the study were healthy, had an uncomplicated pregnancy exceeding 36 weeks gestation and were to be delivered by elective caesarean section because of disproportion or abnormal fetal presentation. All operations were carried out in the morning. The study was approved by the local ethics committee and all participants gave informed consent. The choice of either general or epidural anaesthesia was made by the patient.

All women were given oral antacid treatment consisting of ranitidine, 150 mg, 2–3 h preoperatively, supplemented by 20 ml, 0·3 mol/l

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sodium citrate, immediately before induction. To avoid caval occlusion they were placed in left lateral tilt for 20 min before and during the operation until birth of the infant. An intravenous infusion of a solution of compound sodium lactate BP was set up before commencing anaesthesia, those having an epidural block receiving 1·0–1·5 litres during its establishment. Atropine was not used preoperatively or during the induction sequence in either group.

After 3 min preoxygenation, general anaesthesia was induced with thiopentone, 4 mg/kg, rapidly followed by suxamethonium, 1·5 mg/kg. Cricoid pressure was applied after loss of consciousness and maintained until an endotracheal airway was secured. Anaesthesia was maintained with a mixture of 50% nitrous oxide in oxygen and halothane 0·5%. Pancuronium, 0·08 mg/kg, was given to maintain neuromuscular blockade on recovery from the suxamethonium. Ventilation was controlled to produce normocapnoea, confirmed by measuring end-tidal carbon dioxide content with a 47210 Hewlett-Packard Capnometer. After the umbilical cord was clamped, oxytocin, 10 units, and morphine sulphate, 0·15 mg/kg, were given intravenously, nitrous oxide was increased to 67% and halothane discontinued. At the end of the operation residual neuromuscular block was antagonized with neostigmine, 2·5 mg, and atropine, 1·2 mg. There were 16 women in the general anaesthesia group (GA).

For epidural anaesthesia identification and cannulation of the space was achieved with the patient in the left lateral position. After a test dose of 3 ml of 0·5% bupivacaine without adrenaline, a further 7 ml was injected with the patient sitting up. After 10 min the patient was placed supine in a left tilt and the block extended to T_6 bilaterally, by giving bupivacaine, 1·6 ml per unblocked segment below T_6. Oxygen, 5 l/min, was administered by a Hudson mask before the birth of the baby. Nine women had epidural anaesthesia.

In both groups, heart rate, systolic and diastolic blood pressure were measured and recorded at 5-min intervals throughout the study period using a Dinamap Oscillotonometer commencing at the time of preoperative venous cannulation and ending 2 h after the delivery. Blood samples were collected from the non-infusion arm, control samples being taken at 20 and 10 min before the induction of general anaesthesia or administration of the epidural block. In those women having a general anaesthetic, further sampling was carried out 1 min after tracheal intubation, at uterine incision, and at four 30-min intervals after delivery. In the epidural group, samples were taken at skin incision, uterine incision and at four 30-min intervals after delivery.

Plasma glucose concentration was measured on a Technicon Auto analyser 11 System using the glucose oxidase method. Radioimmunoassay was used to measure the concentrations of plasma insulin, glucagon and cortisol (Riad *et al.* 1979). Blood for catecholamine estimations was immediately centrifuged, the separated plasma was instantly frozen in liquid nitrogen and stored at −20°C until analysed by the method described by Durtieu & Delmotte (1981). For biochemical and cardiovascular data the control samples were pooled. Standard statistical analysis was carried out using the Student's *t*-test for paired data. Probability values <0·05 were regarded as significant.

Results

The two groups (16 GA and 9 epidural) were comparable with regard to age, weight and period of gestation (Table 1) and control values for the cardiovascular and biochemical measurements did not show significant difference. The mean skin to uterine incision times were 6·2 (SD 2·4) min in the epidural group and 8·5 (SD 2·8) min in the general anaesthetic group, while respective values for uterine incision to delivery times were 4·6 (2·7) and 3·6 (4·0) min. Neither of these differences was statistically sig-

Table 1. Physical characteristics of patients in the study

Mode of anaesthesia	*n*	Weight (kg)	Age (years)	Height (cm)
General	16	71·7 (10·0)	29·4 (4·8)	157 (6·9)
Epidural	9	76·1 (17·5)	29·9 (4·4)	161 (6·5)

Results are means (SD).

nificant. In the epidural series one woman required sedation after delivery for a 'dragging sensation' in her subdiaphragmatic region and another required intravenous ephedrine, 15 mg, to maintain her blood pressure. The latter patient did not have catecholamine estimations. No infant in either series required more than routine resuscitative measures at birth, the Apgar scores and time to sustained respiration being closely similar for both groups. Excessive blood loss did not occur and the lowest haematocrit at the end of the study period was 0·32.

Ten of the 16 patients in the GA group required intramuscular opioids for pain relief in the first 30 min after awakening and three more in the following 30 min. The remaining three patients did not require analgesia in the post-operative period of the study. No patient in the epidural group required pain relief — sensory levels to pinprick ranged from T_4 to T_{10} at the end of the study period.

Cardiovascular changes

Marked changes in the cardiovascular variables (Table 2) occurred only within the GA group, the increase in systolic blood pressure and pulse rate in these patients after intubation persisting until 30 min after delivery. Maximal elevation was associated with 'crash' induction and intubation and it was only at this time that the rise in diastolic blood pressure was statistically significant. The decreases in heart rate, systolic and diastolic pressure within the epidural group were not statistically significant or clinically important except in the one patient who required ephedrine for hypotension.

Catecholamines

Catecholamine estimations were obtained from six patients given a general anaesthetic and four patients given an epidural block. The control values [mean (SD) pg/ml] in the GA and epidural groups for adrenaline were 141 (34·9) and 111 (56·0) and for noradrenaline 386 (125) and 330 (58·1) respectively, neither of the differences was statistically significant.

Figure 1 shows the percentage change from control values: there were marked differences between the groups, the GA patients showing a dramatic increase and those given epidural a decrease in both adrenaline and noradrenaline levels. Variations in the GA series were most marked during the induction to delivery interval, the increases in adrenaline greatly exceeding those of noradrenaline. Statistical differences in adrenaline levels were significant at induction, uterine incision and 30 min after delivery ($0{\cdot}001<P<0{\cdot}01$ in each case). Noradrenaline differences were statistically significant at induction ($P<0{\cdot}01$), uterine incision ($P<0{\cdot}05$) and 60 and 90 min after delivery ($P<0{\cdot}02$). Plasma catecholamine levels had returned to near control values by 120 min of the epidural block.

Plasma cortisol, glucose and insulin

The variations in plasma cortisol and glucose are shown as absolute values (Fig. 2). The mean

Table 2. Percentage changes from pre-operative control values of cardiovascular measurements during and after caesarean section

Anaesthesia	Cardiovascular variable	Control values	Percentage change at observation times (min)					
			PI*	UI†	30	60	90	120
	Blood pressure (mmHg)							
General	Systolic	133 (4)	+19 (5)	+17 (4)	+6 (4)	0 (4)	−6 (4)	−6 (3)
(n=16)	Diastolic	90 (3)	+20 (5)	+10 (7)	−8 (5)	−5 (5)	−10 (5)	−11 (4)
	Heart rate (beats/min)	90 (4)	+26 (5)	+44 (6)	+21 (6)	−3 (6)	−12 (3)	−9 (4)
	Blood pressure (mmHg)							
Epidural	Systolic	127 (3)	+1 (4)	+2 (4)	−7 (4)	−8 (3)	−7 (2)	−7 (2)
(n=9)	Diastolic	82 (3)	−5 (3)	−7 (3)	−18 (5)	−11 (5)	−9 (5)	−6 (5)
	Heart rate (beats/min)	88 (4)	−12 (4)	−4 (5)	−11 (5)	−11 (6)	−14 (5)	−13 (5)

*PI at skin incision; †UI at uterine incision.
Results are means (SEM).

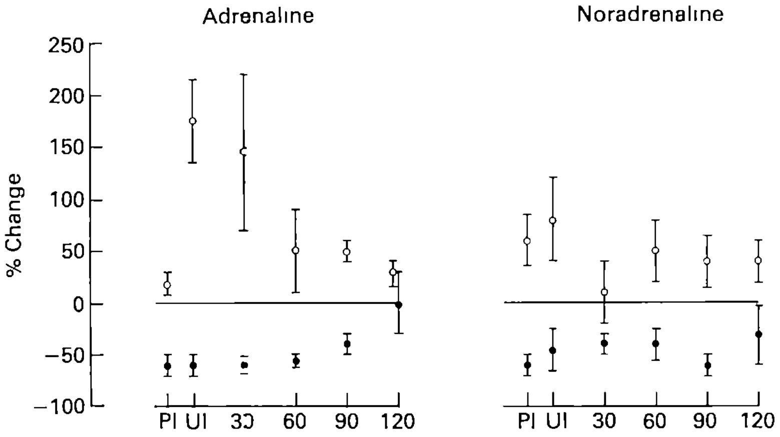

Fig. 1. Percentage changes (mean ± SE) from pre-operative control values of plasma adrenaline and noradrenaline levels associated with general (○, $n = 6$) and epidural (●; $n = 4$) anaesthesia. Samples were obtained at skin incision (PI), uterine incision (UI) and at 30-min intervals after delivery

control values of insulin in the GA and epidural groups were 5·8 (SD 2·0) μU/ml and 8·5 (SD 8·1) μU/ml respectively and were not statistically different ($0{\cdot}05<P<0{\cdot}10$). Because of the marked scatter of control readings in the epidural series alterations in insulin levels are presented as percentage change from control values in Fig. 2. Whereas plasma cortisol levels decreased after induction in both groups, a sustained rise followed in the GA patients and the differences between the series at 30 ($P<0{\cdot}001$), 60, 90 and 120 ($P<0{\cdot}02$) min were statistically significant. In the patients having epidural anaesthesia, plasma glucose levels were unchanged throughout the period of study, but general anaesthesia was associated with significant elevation from 30 min onwards ($P<0{\cdot}001$). Induction of general anaesthesia was associated with an 84% rise in plasma insulin compared with a 4% increase in the epidural group ($P<0{\cdot}01$), the latter showing little variation throughout. However, at 60–120 min significant increases ($P<0{\cdot}02$) in insulin level occurred in GA patients. The changes in plasma glucagon levels were not statistically significant irrespective of the method of anaesthesia and are not presented.

Discussion

While the use of regional or general anaesthesia for caesarean delivery is often dependent on the patient's wishes her choice can be influenced by the viewpoints of the obstetrician or the anaesthetist. In recent times there has been a greatly increased use of epidural block mainly because of the risk of aspiration pneumonitis associated with general anaesthesia. In a healthy pregnancy, infant well-being seems to be little influenced by the method selected. While additional factors such as satisfaction, immediate bonding with her baby and the prospect of post-delivery analgesia with epidural are of great importance, many women and their attendants require more factual evidence of its advantages.

All anaesthetists are agreed that the rapid establishment of an endotracheal airway is essential for the safe management of general anaesthesia for delivery and that it is best carried out in a very light plane of anaesthesia in a totally paralysed patient. In such circumstances laryngoscopy and intubation have been shown to provoke marked cardiovascular changes in the non obstetric patient (Russell *et al.* 1981). These may be reduced or obtunded by the intravenous administration of large doses of fentanyl (Stanley *et al.* 1980) or morphine (Hoar *et al.* 1981), neither of which would be acceptable medication in the pre-delivery phase of an obstetric anaesthetic. The pattern of induction of general anaesthesia used in this investigation is that most commonly practised and was associated with hypertension and tachycardia throughout the operative period. The effects of these changes on the healthy woman are probably not great but where her cardiovascular system is

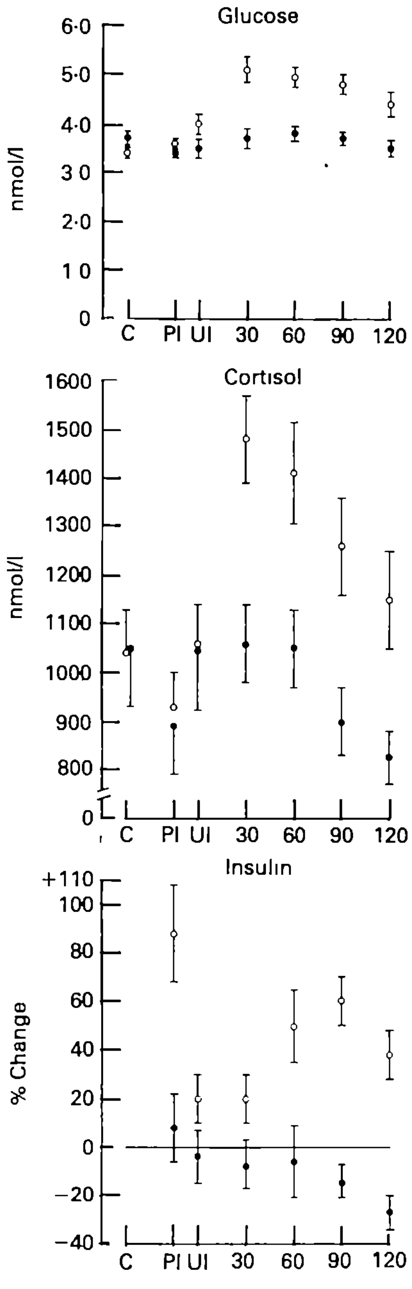

Fig. 2. Plasma glucose and cortisol levels (mean ± SE) and percentage change in insulin levels (mean ± SE) associated with general (○, n = 16) and epidural (●; n = 9) anaesthesia. Samples were obtained before induction of anaesthesia (C), at skin incision (PI), uterine incision (UI) and at 30-min intervals after delivery. Mean control values (C) for plasma insulin were 5·79 (SE 0·45) μU/ml for general and 8·5 (SE 2·66) μU/ml for epidural anaesthesia

already compromised by disease or anomaly or there is a pre-existing hypertensive condition a critical situation could result. Epidural anaesthesia given by the method advocated by Crawford (1982) and Thorburn & Moir (1980), and with fluid preloading, caused a more controllable response suggesting that it would be preferable in such patients.

The difference in the reported cardiovascular response between the GA and epidural series was associated with marked differences in plasma catecholamine levels. Derbyshire *et al.* (1983) demonstrated a significant elevation in plasma noradrenaline concentration associated with the pressor response to intubation and if suxamethonium was used, plasma adrenaline levels increased significantly as well. In the present study the high post-induction levels of catecholamine were probably related to laryngoscopy and intubation, and the continuing increased level during the operative period to the light levels of general anaesthesia used until delivery.

The low levels of noradrenaline and adrenaline found in the epidural group confirm the findings in other non-obstetric studies (Hall 1985). The decreased output of adrenaline, due to blockade of the innervation of the adrenal medulla, inhibited the hyperglycaemic response to surgery. Engquist *et al.* (1977) reported the total abolition of the glucose and cortisol response could be achieved by neuronal blockade from T_4 and S_5 in patients undergoing hysterectomy but less extensive blockade, while still producing excellent analgesia and operating conditions, failed to inhibit completely the increase in plasma cortisol. Despite the fact that caesarean section is a much less stimulating operation than hysterectomy, patients given general anaesthesia showed marked elevation of glucose and cortisol levels. While the successful use of epidural anaesthesia requires a neuronal blockade to at least the T_8 dermatome (Crawford 1982) and gentleness on the part of the surgeon, the profound depression of the neuroendocrine response in our patients suggests a higher level of sympathetic nerve blockade.

Insulin secretion is usually inhibited by both general anaesthesia (Traynor *et al.* 1982; Buckley *et al.* 1982) and raised catecholamine levels (Porte & Robinson 1973). In the present study, however, a sudden rise at induction of general anaesthesia occurred and this may have been due to the cholinergic effect of suxamethonium in the absence of atropine premedication as such stimulation enhances insulin secretion (Kajinuma *et al.* 1968). However, as none of our patients showed other evidence of cholinergic activity this finding requires further investigation. The low levels of plasma insulin in the epidural series concur with the findings of Halter & Pflug (1980) who showed that in patients under high, as distinct from low, spinal blockade, the insulin response to a glucose load was suppressed. These workers concluded that integrity of the sympathetic innervation (T_6 to T_{10}) to the pancreas was essential for normal pancreatic islet function.

The relevance of these findings to the choice of anaesthesia for caesarean delivery is difficult to assess as this investigation was carried out in healthy women with a normal mature pregnancy. The lesser cardiovascular upset associated with epidural block suggests that its use is strongly indicated where cardiac anomaly or hypertension are present. This, however, presumes that the administration is expertly managed and that the block is instituted in a slow controlled manner with attention to monitoring, fluid loading and use of vasopressor drugs. The obtunded neuroendocrine response associated with epidural block should facilitate the perioperative management of those patients suffering from endocrine or metabolic disorders. We have not studied fetal welfare but Shnider *et al.* (1979) have shown that elevated catecholamine levels prejudice placental perfusion Jouppila *et al.* (1978) showed that if hypotension was avoided, placental blood flow did not decrease during caesarean section with epidural anaesthesia. Both studies together with our findings suggest that infant well-being should be at lesser risk with the regional technique.

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Vaginal and abdominal delivery increases maternal urinary 6-keto-prostaglandin $F_{1\alpha}$ excretion

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Summary. To study the role of the antiaggregatory and vasodilatory prostacyclin (PGI_2) during human delivery, serial urine samples collected from 13 women delivered vaginally and from eight delivered abdominally were assayed for 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$, a breakdown product of PGI_2) by high-performance-liquid-chromatography and radioimmunoassay. In women delivered vaginally the mean urinary 6-keto-$PGF_{1\alpha}$ concentration was 41·9 (SE 8·3) ng/mmol creatinine, before the onset of labour and increased progressively to a maximum of 186·5 (SE 47·6) ng/mmol creatinine 2 h after delivery irrespective of the use of oxytocin and epidural analgesia. In women delivered by caesarean section under epidural anaesthesia, the urinary 6-keto-$PGF_{1\alpha}$ rose from 33·4 (SE 4·2) ng/mmol creatinine to 2153 (SE 314) ng/mmol creatinine 2 h after section. In both groups the increased levels had fallen by 24 h postpartum to levels below those found before delivery. In neonatal urine 6-keto-$PGF_{1\alpha}$ concentrations were some 12–30 times higher than those in postpartum urine. Thus, vaginal and abdominal delivery is accompanied by significant increases in maternal PGI_2 release, perhaps in the myometrium and/or intrauterine tissues. This may be of significance in the regulation of fetoplacental blood flow and in the prevention of intra- and postpartum thrombosis.

Vaginal and abdominal delivery is accompanied by rises of maternal plasma 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$), a stable breakdown product of the antiaggregatory and vasodilatory prostacyclin (PGI_2) (Ylikorkala *et al.* 1981, 1982). This has been taken as evidence of increased release of PGI_2 during delivery, which may control uteroplacental blood flow, or prevent thrombosis during and after labour. Since these findings, the validity of 6-keto-$PGF_{1\alpha}$ in plasma as an index of PGI_2 synthesis *in vivo* has been questioned, especially when low values are being measured (Blair *et al.* 1982), and thus the role of PGI_2 during labour needs to be ascertained. A great deal of recent evidence suggests that urinary 6-keto-$PGF_{1\alpha}$ excretion reflects reliably in-vivo PGI_2 synthesis (Zipser & Martin 1982; Nadler *et al.* 1983; Fischer *et al.* 1982; Casey *et al.* 1983; Jouppila *et al.* 1985). Therefore to further clarify the role of PGI_2 in labour, we measured urinary excretion of 6-keto-$PGF_{1\alpha}$ in the mothers and newborn infants in association with vaginal and abdominal delivery.

Subjects and methods

Twenty-one healthy women with uncomplicated normotensive pregnancies were studied with the

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approval of the local ethics committee (Table 1). Labour started spontaneously in 13 women who were delivered vaginally. Seven of them received intravenous oxytocin to augment uterine contractions and five epidural analgesia to relieve pain in labour. Eight women with fetopelvic disproportion were delivered by elective caesarean section under epidural anaesthesia induced with 0·5% bupivacaine (14–26 ml). Oxygen (2 litres/min) was administered through an intranasal catheter. All women were kept in 20° left lateral tilt from the induction of anaesthesia to the birth of the infant to avoid aortocaval compression. All infants were healthy and born in good condition.

Samples

Urine samples (20 ml) were collected from the women delivered vaginally as follows: before and in the presence of regular contractions; when the cervix was 5 cm and 10 cm dilated; at 2 h, 6 h and 24 h postpartum (Fig. 1, Table 2). From women having a caesarean section, urine samples were collected through a bladder catheter at the following times: before the onset of anaesthesia and at 1, 3, 6, 9, 12, 15 and 24 h after the incision (Fig. 2). In addition, the first neonatal urine was collected into a plastic bag from all infants. The urine samples were frozen (−25°C) until assayed for 6-keto-$PGF_{1\alpha}$.

Measurement of 6-keto-$PGF_{1\alpha}$

A urine sample (5 ml) was acidified to pH 3·0 with HCl 1 mol/l and passed through an octadecylsilyl silica cartridge (Sep-Pak C 18 Cartridges Waters Ass., Inc., Milford, Massachusetts, USA), prewashed successively with 5 ml of ethanol, water and acetic acid (0·1 mol/l). The cartridge was then washed with 15% ethanol (5·0 ml) in water and petroleum ether (5·0 ml). The 6-keto-$PGF_{1\alpha}$ absorbed was eluted in 2 ml of ethylacetate and evaporated to dryness under a nitrogen stream. The sample was further purified with high pressure liquid chromatography (Spectra Physic M-740, Santa Clara, California, USA) utilizing a Sherisorb 5 u ODs II column (Phase Separations Ltd, Industrial Estate Queensberry CLWD, UK) and a mobile phase of water: acetic acid 69:95–30·0:0·05 with a flow rate of 2 ml/min. 6-keto-$PGF_{1\alpha}$ eluted at 3 min and separated totally from other prostanoids. The fraction containing 6-keto-$PGF_{1\alpha}$ was evaporated to dryness and redissolved in phosphate buffered saline with 0·1% of gelatin. Two different size aliquots, both in duplicate, were taken for radioimmunoassay, as described elsewhere (Ylikorkala & Viinikka 1981). The mean recovery of 6-keto-$PGF_{1\alpha}$ added to urine (200–400 pg/ml) was 79·6(SD 8·9)% in 10 samples and the interassay variation was 10·8% after the whole procedure. The urinary 6-keto-$PGF_{1\alpha}$ excretion measured with this method decreased by 55% in 15 patients with rheumatoid arthritis during indomethacin (75 mg daily) and it increased 5–10 fold in pre-eclamptic women whose blood pressure was controlled with intravenous infusion of PGI_2 (up to 8 ng/kg/min) (Jouppila *et al.* 1985). The result is given as nanograms of 6-keto-$PGF_{1\alpha}$/mmol of creatinine which was determined by a routine method.

Statistical methods

The results were subjected to the paired and non-paired *t*-test and linear regression analysis.

Table 1. Clinical data of the study populations

	Vaginal delivery	Abdominal delivery
Number of women	13	8
Maternal age (years)	30·7 (1·4)	31·9 (2·0)
Parity		
Nulliparous (*n*)	10	4
Parous (*n*)	3	4
Gestational age at delivery (weeks)	39·4 (1·8)	40·6 (1·2)
Birthweight (g)	3639 (126)	3835 (170)

Results are means (SE).

Results

Maternal 6-keto-$PGF_{1\alpha}$

The initial 6-keto-$PGF_{1\alpha}$ excretion in women delivered vaginally did not differ significantly from that in women having a caesarean section (Table 2). Vaginal delivery was accompanied by a progressive rise in urinary 6-keto-$PGF_{1\alpha}$ with the maximum level (about 4·5 times the initial one) occurring at 2 h postpartum (Fig. 1, Table 2). This rise was independent of the use of oxytocin and/or epidural analgesia. The urinary 6-keto-$PGF_{1\alpha}$ concentration decreased gradually after delivery so that the level at 24 h was

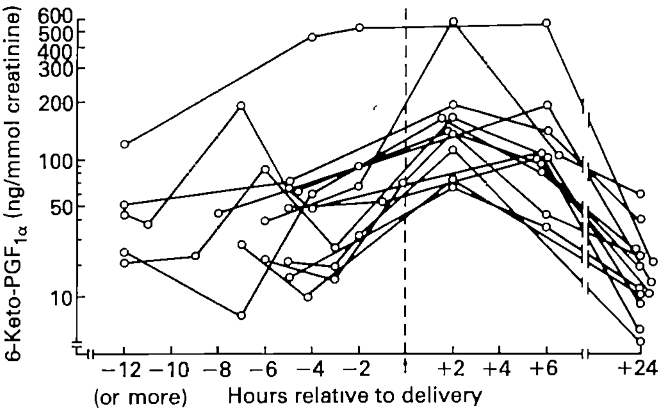

Fig. 1. Maternal urinary excretion of 6-keto-prostaglandin $F_{1\alpha}$ in association with vaginal delivery at term Note the logarithmic scale for 6-keto-$PGF_{1\alpha}$.

lower than that before the onset of labour (Table 2).

During abdominal delivery 6-keto-$PGF_{1\alpha}$ increased to the maximum of about 65 times the initial value at 3 h after the incision (Fig. 2, Table 2). The urinary 6-keto-$PGF_{1\alpha}$ then fell gradually and was lower at 24 h than before incision, and lower than the corresponding level in the women delivered vaginally (Table 2).

Neonatal 6-keto-$PGF_{1\alpha}$

In the first neonatal urine the concentration of 6-keto-$PGF_{1\alpha}$ was some 6–10 times higher than in the maternal urine before delivery and some 12–30 times higher than in maternal urine 24 h postpartum. The neonatal urine 6-keto-$PGF_{1\alpha}$ tended to be higher in infants born abdominally than in those born vaginally. It was not related to the initial or maximal maternal 6-keto-$PGF_{1\alpha}$ level nor to the use of oxytocin and epidural analgesia in vaginal deliveries.

Discussion

The origin of urinary metabolites of PGI_2 is not definitely known; some data suggest a wholly renal origin, while others indicate an additional extrarenal contribution (Zipser & Martin 1982; Fischer *et al.* 1982; Nadler *et al.* 1983; Casey *et al.* 1983; Jouppila *et al.* 1985). In the present study the urinary 6-keto-$PGF_{1\alpha}$, a non-enzymatic metabolite of PGI_2, rose conspicuously during vaginal and even more during abdominal delivery. Since there is no reason to presume a change in renal physiology that could result in these large increases in urinary 6-keto-$PGF_{1\alpha}$ levels, our data strongly suggest that the urinary 6-keto-$PGF_{1\alpha}$ originates from extrarenal sources in addition to the kidneys. Thus our data favour the view that urinary PGI_2 metabolites reflect well the overall synthesis of PGI_2 in the body.

Table 2. Maternal and neonatal 6-keto-$PGF_{1\alpha}$ excretion in association with vaginal and abdominal delivery (ng/mmol of creatinine, mean±SE)

	Urinary 6-keto-$PGF_{1\alpha}$ concentrations	
Time of sampling	Vaginal delivery	Abdominal delivery
No. of patients	13	8
Before onset of labour or anaesthesia	41·9 (8·3)	33·4 (4·2)
In presence of regular contractions	48·3 (23·9)	—
Cervical dilatation		
5 cm	124·2 (53·7)^{a}	—
10 cm	129·5 (61·2)^{a}	—
Time after vaginal delivery or incision		
1 h	—	925 (207)^{b}
2 h	186·5 (47·6)^{b}	2153 (314)^{b,d}
6 h	138·8 (37·1)^{b}	649 (110)^{b,d}
24 h	21·6 (4·5)^{a}	10·5 (4·9)^{a,c}
First neonatal urine	250·0 (48·4)	354·7 (110.0)

Significance of differences

Compared with 'before' value: a = $P<0·01$, b = $P<0·001$

Compared with vaginal delivery: c = $P<0·01$, d = $P<0\ 001$

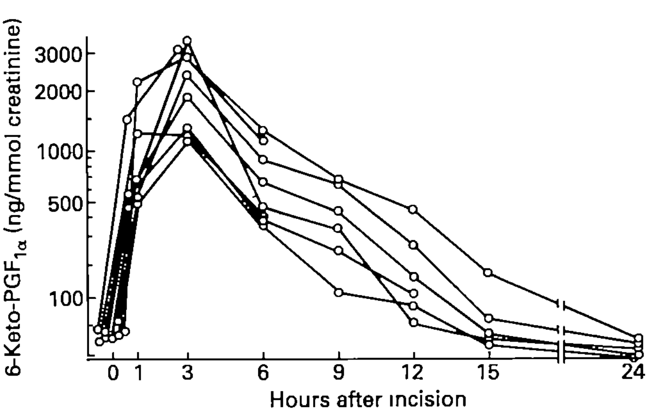

Fig. 2. Maternal urinary excretion of 6-keto-prostaglandin $F_{1\alpha}$ before, during and after caesarean section Note the logarithmic scale for 6-keto-$PGF_{1\alpha}$.

Our present finding is in general agreement with previous data obtained by 6-keto-$PGF_{1\alpha}$ measurements in maternal plasma (Ylikorkala *et al.* 1981, 1982) or amniotic fluid (Mitchell *et al.* 1979; Mäkäräinen & Ylikorkala 1984). However, the increment of 6-keto-$PGF_{1\alpha}$ in maternal urine was about 6–8 times larger than that in plasma during vaginal delivery and some 13–20 times greater than during caesarean section (Ylikorkala *et al.* 1982). Thus urinary 6-keto-$PGF_{1\alpha}$ levels reveal much larger changes in PGI_2 production during delivery than expected from rises in plasma levels. Our present data show that the measurement of urinary 6-keto-$PGF_{1\alpha}$ is a more sensitive index of PGI_2 synthesis *in vivo,* and when increased PGI_2 production is to be measured.

The origin of the increased urinary 6-keto-$PGF_{1\alpha}$ during delivery could be the maternal vascular bed, kidneys, or the myometrium and/or intrauterine tissues, which are all capable of producing PGI_2 *in vitro,* as reviewed recently (Ylikorkala & Mäkila 1985). Because the manipulation and traumatization of the myometrium and intrauterine tissues is more extensive during caesarean section than vaginal delivery, the higher rise of urinary 6-keto-$PGF_{1\alpha}$ during caesarean section suggests the uterine compartment as a source of increased PGI_2-production. Further support for this speculation comes from the fact that the urinary 6-keto-$PGF_{1\alpha}$ excretion was higher in the pregnant than non-pregnant state. The physiological significance of delivery-induced PGI_2 rise is unknown, but in theory it could be of significance in the prevention of intra- and postpartum thromboembolic complications and in the regulation of the uteroplacental circulation.

Neonatal urine contained more 6-keto-$PGF_{1\alpha}$ than maternal urine, which is in good agreement with the data that the fetal and/or neonatal tissues produce more PGI_2 than the corresponding adult sources (Coceani & Olley 1982). This finding is also in harmony with the very high levels of 6-keto-$PGF_{1\alpha}$ on the first day of life in plasma (Kaäpa *et al.* 1982) or urine (Seyberth *et al.* 1984). In contrast to Casey *et al.* (1983), we did not find higher urinary 6-keto-$PGF_{1\alpha}$ levels in infants born vaginally than in those born by section. It is possible that we failed to obtain the very first urines probably with the highest 6-keto-$PGF_{1\alpha}$ levels in some vaginally born infants, because they often urinated immediately after birth and before the urine could be collected.

In conclusion, maternal urinary 6-keto-$PGF_{1\alpha}$ rose during vaginal and abdominal delivery, reflecting increased PGI_2 release most likely in the myometrium and/or intrauterine tissues.

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Antenatal diagnosis of placental anastomosis in a twin pregnancy using Doppler ultrasound

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Summary. Qualitative analysis of blood velocity in the umbilical arteries of twin fetuses detected by pulsed Doppler ultrasound revealed discordant patterns which permitted an accurate antenatal diagnosis of an artery-to-artery anastomosis. One twin was consistantly larger than the other, had a normal umbilical artery impedance and survived; the other fetus was consistantly smaller, had persistantly high umbilical artery impedance and died *in utero*. The death of one fetus did not affect the blood flow patterns within the umbilical artery of the other up to delivery 24 h later. The case demonstrates that intrauterine morbidity due to vascular anastomoses is not confined to the transfusion of significant amounts of blood from one fetus to another.

Pulsed Doppler ultrasound permits a non-invasive means of measuring the velocities of red blood cells within deeply situated human blood vessels (Atkinson & Woodcock 1982). Qualitative analysis of the patterns of arterial red blood cell velocities over the cardiac cycle provides information about the distal impedance to blood flow (Woodcock & Skidmore 1980) and the technique has been applied to the human umbilical artery where impedance has been found to be abnormally high in growth retarded fetuses (Erskine & Ritchie 1985). During studies on the significance of altered umbilical artery impedance, the following case was noted.

Patient and methods

A 37-year-old married white woman (para 3 + 1) presented at the antenatal clinic at 8 weeks gestation in her fifth pregnancy. Her first three pregnancies all ended in spontaneous vaginal deliveries; the first was a 2320 g normal female at 36 weeks gestation, the second a 2500 g normal female at term and the third a 2720 g normal female also at term. The fourth was a tubal ectopic pregnancy resulting in salpingectomy.

The patient smoked 20 cigarettes per day but had no other personal or family history of significance.

At the first antenatal visit the blood pressure was 110/70 mmHg; a vaginal examination confirmed a gravid uterus consistent with 8 weeks amenorrhoea. On routine ultrasound scanning at 16 weeks amenorrhoea a twin pregnancy was detected and fetal maturity was confirmed.

At both 14 and 16 weeks her blood pressure was 160/90 mmHg. Two weeks later it was 160/110 mmHg. She was admitted to hospital and during her 6 day stay her blood pressure stabilized at 140/90 mmHg. She was readmitted at 28 weeks again with hypertension and remained in hospital until delivery. Blood pressure was labile, the diastolic pressure usually being 90 mmHg, but rising for short periods to 160/120 mmHg. Antihypertensive therapy was not given. Realtime ultrasound at 28 weeks revealed differences between the two fetuses in head and abdominal diameters, but serial measurements thereafter showed a normal growth rate of the smaller twin (Fig. 1). Antenatal cardiotocography of the larger twin remained normal, but tracings were always difficult to obtain from the smaller fetus which consistently lay transversely

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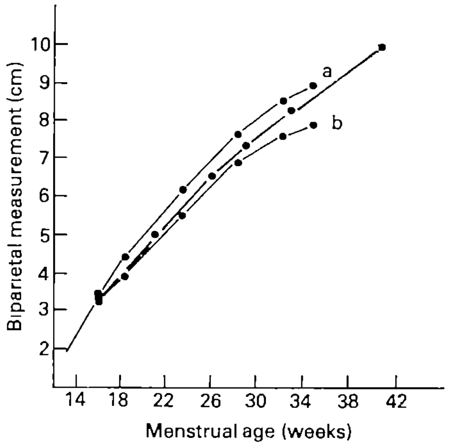

Fig. 1. Serial biparietal measurements of the larger fetus (a) and the smaller fetus (b) in a twin pregnancy. Values for the 50th centile of normal singleton fetus are also given.

and low within the uterus and all heart rate tracings from this fetus were virtually impossible to interpret.

At 36 weeks gestation no fetal heart movement in the smaller twin could be detected by a further ultrasound scan although it had been present 24 h earlier.

Elective caesarean section was performed the following day. The first twin was a stillborn female infant and weighed 1755 g. Post mortem examination detected no cardiac or other abnormality. The second liveborn female twin weighed 2320 g and had Apgar scores of 3 and 9 at 1 min and 9 min respectively; the baby continued to thrive. There was a single placenta. Cord blood was taken from the surviving twin and the haemoglobin estimation was 16·3 g/dl with a haematocrit of 49%. M-mode echocardiography of this twin at 6 h of age detected no abnormalities.

Inspection of the monochorionic diamniotic placenta showed a vessel coursing over the fetal surface linking together an umbilical artery of each cord. This was confirmed by subsequent X-ray contrast angiography (Fig. 2). In addition, the larger twin's portion of the placenta was approximately two-thirds of the whole organ, with the remaining one-third belonging to the smaller fetus. These portions of the placenta were also different in texture, with more calcification present in the smaller portion. Subsequent histological examination revealed no further useful information.

Doppler technique

Umbilical artery blood flow studies were carried out serially as part of a research programme using a range-gated pulsed Doppler ultrasonic sector scanning system (Advanced Technology Laboratories, Mark V) with a 3 Mz probe. The method has been previously described (Erskine & Ritchie 1985). Umbilical artery impedance was estimated by calculation of the pulsatility index (PI) as shown in Fig. 3 and the mean value from each tracing was calculated from 10 consecutive waveforms.

The fetuses always remained in the same orientation to each other and thus sampling was performed on the same portions of the cords at all times. In any case, the difference between the cord blood flows was so easily apparent both visually and audibly that eventually the patient herself could identify the relevant fetus without confirmation by real time ultrasound.

Doppler examinations

Twenty-three Doppler scans were performed over a period of 53 days. The larger fetus consistently had normal umbilical artery sonograms (Fig. 4) with PI values in the normal range. The umbilical artery sonograms of the smaller fetus were always changing in a cyclical manner such that episodes of low impedance with forward blood flow in diastole were immediately followed by periods of absent and, on occasion, even reverse flow during diastole (Fig. 5). The PI was calculated as described previously but in the smaller fetus, because of cyclical variation, the PI was calculated from the 10 consecutive waveforms which contained the greatest end-diastolic forward flow, so as to achieve the lowest possible value for impedance in each tracing. The PI for the larger twin was almost always within the normal range, whereas that of the smaller twin showed cyclical variation but was almost always in the abnormal range (Fig. 6).

The cyclical nature of the smaller twin's blood flow pattern could only be explained antenatally by an arterial anastomosis between the fetuses such that the smaller twin's umbilical blood flow had to 'give way' to that of the larger twin when both cardiac cycles coincided. Thus it was only when the cycles were asynchronous that the smaller fetus could achieve forward blood flow at the end of diastole.

The surviving twin's blood flow pattern and

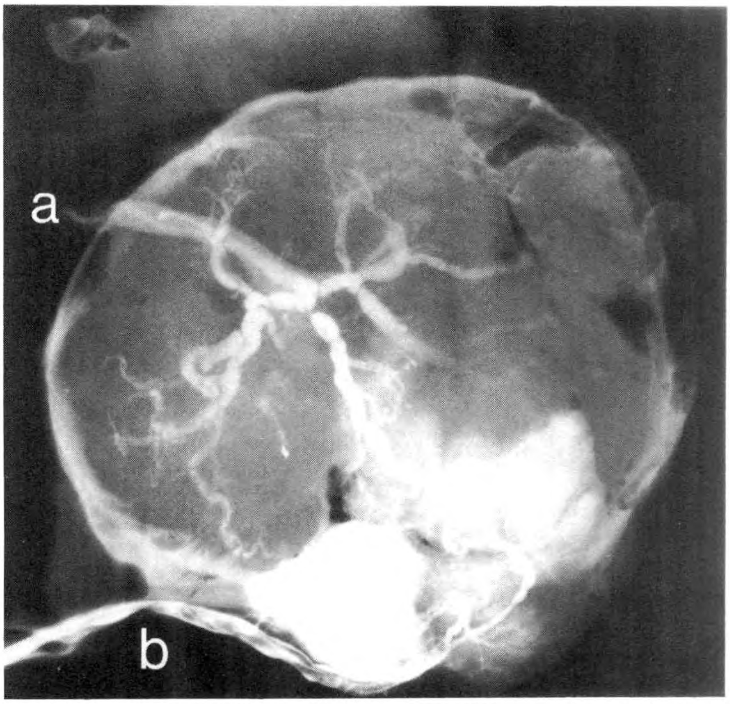

Fig. 2. X-ray of the placenta in the twin pregnancy with contrast medium emerging into the cord of the larger twin (a) after injection into an artery of the smaller twin (b). The anastomosis between the two cords is apparent.

heart rate were normal on two occasions 24 h apart after the death of the smaller fetus.

Discussion

Although vascular connections have been described in fused dichorionic placentas (Strong & Corney 1967), doubt has been cast on the true zygosity of most of these anastomoses (Morison 1970). The incidence of vascular anastomoses in monochorionic placentas is approximately 84% (Strong & Corney 1967) but the clinical effect of such a link between twins ranges from the undetectable to the classical plethoric polycythaemic fetus in association with a smaller pale anaemic twin—the first being a recipient of blood transfer and the second being the donor.

Many types of anastomoses can occur, ranging from the simple artery-to-artery linkage to multiple combinations of vein-to-vein, artery-to-artery and artery-to-vein as well as anastomoses within the capilliary bed (Morison 1970) and the physiological effect will thus vary widely. An artery-to-vein communication will cause polycythaemia in the recipient. The resultant anaemia of the donor stimulates further red cell production via erythropoietin and this hormone will also reach the polycythaemic twin and stimulate its red cell production, further exacerbating the situation. This mechanism is probably that which results in the death of one twin in the early second trimester.

The chronic donor/recipient syndrome varies in severity, not only with the size of the linkage but also with the presence of other anastomoses, some of which may compensate others by allow-

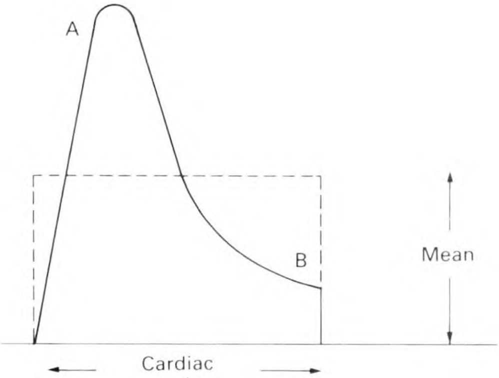

Fig. 3. Measurements required from umbilical artery sonograms in order to calculate the pulsatility index (A − B/mean).

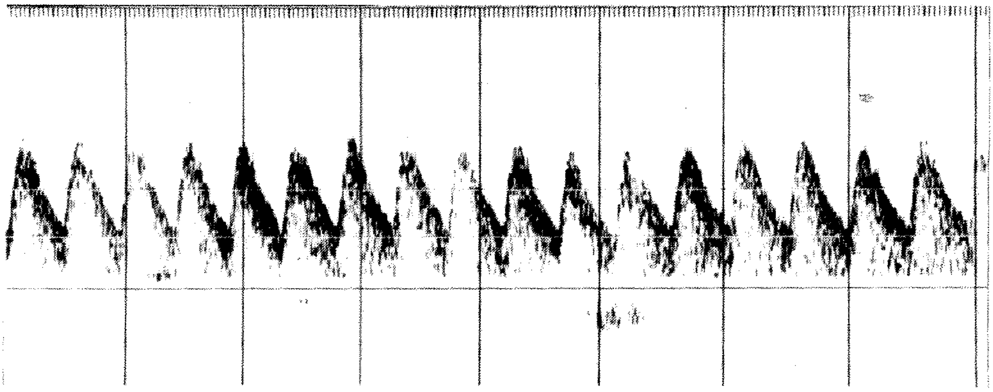

Fig. 4. Normal umbilical artery time-velocity waveforms (sonograms) obtained from the larger fetus of the twin pregnancy.

ing the recipient twin to transfer blood back to the original donor fetus. The precise anatomical configuration in any specific case can therefore be very complex. In addition, transfusions can occur acutely at the time of delivery, complicating the neonatal findings and thus further masking the true intrauterine circumstances.

In the case presented the smaller twin died *in utero*, yet the surviving twin had both a normal cord blood haemoglobin and haematocrit. Without the knowledge provided by the Doppler studies the explanation of the death of the smaller twin in the apparent presence of only an artery-to-artery anastomosis without significant transfusion having occurred would have been very difficult, if not impossible. The high umbilical artery impedance in the smaller twin resulting from an arterial anastomosis to a dominant twin provides a simple mechanism to explain the death of the smaller twin through raised cardiac workload.

In only 15% of monochorionic twin pregnancies do significant twin-to-twin transfusions occur (haemoglobin differences of at least 5 g/dl) although strong suspicions may exist in another 15% of cases (Strong & Corney 1967). However, twin fetuses can still be compromised, as in the case presented, without differences in haemoglobin concentrations. The definition of twin-to-twin transfusion as based on cord blood haemoglobin differences of at least 5 g/dl (Oski & Naiman 1982) should no longer be used as a test of the presence or absence of physiologically significant twin-to-twin vascular anastomoses.

The Doppler studies permitted an accurate and definitive diagnosis to be made antenatally of an arterial anastomosis between a set of twin fetuses. There are only two reports in the literature of vascular connections between twins being diagnosed before delivery (Wittman *et al.* 1981; Brennan *et al.* 1982) but both these diagnoses were presumptive and relied upon the following criteria as detected by real time ultrasound: the twins were of the same sex; their growth rate was significantly different; there were differences in amniotic sac volumes, and

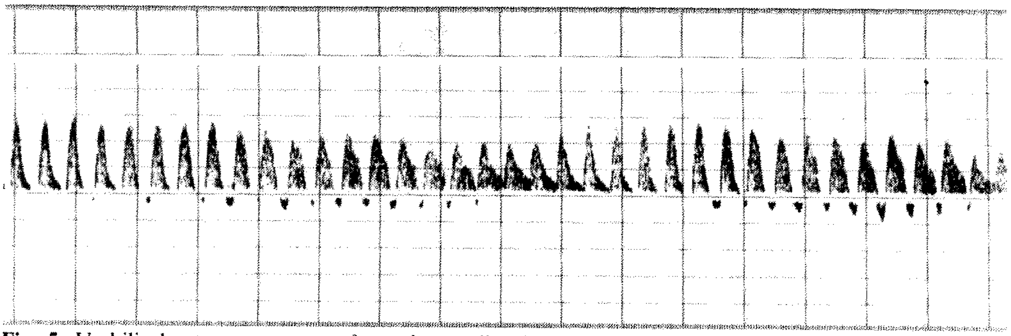

Fig. 5. Umbilical artery sonograms from the smaller fetus in a twin pregnancy demonstrating a cyclical alteration of blood flow patterns during diastole ranging from absent through reverse to forward flow.

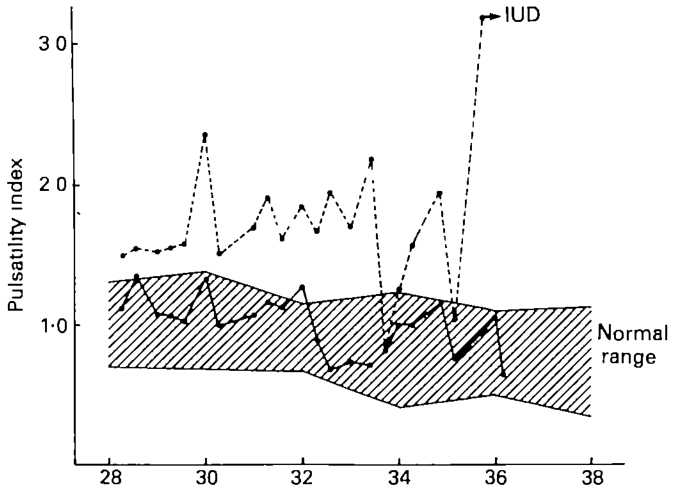

Fig. 6. Serial values for umbilical artery pulsatility index (PI) for the fetuses of a twin pregnancy superimposed on the normal range. The smaller twin with the higher impedance died *in utero* at 36 weeks gestation

there was a single placenta consisting of two portions, discordant both in their size and echogenicity.

The Doppler technique, on the other hand, detected not only obvious differences in flow patterns within the actual umbilical arteries, but also differences which were of a cyclical and dynamic nature which could only arise if both arteries were linked. This is the first time that a vascular connection between twins has been definitively diagnosed antenatally and the technique holds promise for the antenatal surveillance of twin pregnancies which has proved difficult by other conventional means.

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Haemolytic disease of the newborn—the changing scene

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Summary. Between 1950 and 1970 there was a steady decline in the number of infant deaths from rhesus haemolytic disease of the newborn in the Yorkshire Region but no decrease in the number of pregnant women with antibodies. Following the introduction of Rh prophylaxis in 1970, the number of pregnant women sensitized has decreased by 70% and the number of infant deaths by 96%. The number of infants requiring exchange transfusion has also decreased by 70%. During the years 1980 to 1983 there were 163 new cases of maternal sensitization to the D antigen in the Yorkshire Region, 36 were due to failures of administration, 75 were failures of protection and 26 were in primigravidae. Eighteen of the failures of administration occurred after abortion, nine of which were surgical terminations. Antenatal prophylaxis may well have protected 64 (40%) of these 163 women. The number of pregnant women with antibodies other than anti-D now exceeds those with anti-D. The effect of these changes in incidence and clinical severity on the management of Rh D negative pregnant women is discussed.

Between the years 1950 and 1970 rapid improvements in the management of pregnant women and their infants with rhesus (Rh) haemolytic disease of the newborn resulted in a steady decline in infant morbidity and mortality from around 1·5 to 0·5 deaths/1000 births. This occurred because of the introduction of exchange transfusion, amniocentesis, premature delivery and intrauterine transfusion. However, during these years there was no decrease in the number of pregnant women with antibodies to the Rh or any other blood group antigen.

The introduction of post delivery anti-D immunoglobulin prophylaxis dramatically changed the clinical picture and from 1970 to 1976 the number of women developing anti-D antibodies decreased considerably (McMaster Conference 1979; Tovey *et al.* 1978). Unfortunately, since 1976 this decline has almost ceased (Fig. 1), and the reasons have been described by a number of workers (McMaster Conference 1979; Eklund 1982; Tovey & Taverner 1981). An analysis of the cases encountered in the Yorkshire Region between 1980 and 1983 illustrates clearly why we are continuing to encounter new cases of maternal sensitization in spite of Rh prophylaxis (Table 1). This study investigated the clinical circumstances resulting in these new cases, and the attempts being made to reduce the prevalence. The data also illustrate the need for changes in the clinical services provided for the management of pregnant women with Rh antibodies, and finally the contribution of blood group antibodies, other than anti-D, to the occurrence of haemolytic disease of the newborn. Haemolytic disease due to ABO has not been included in this survey. The area covered has a population of 3·2 million with approximately 40 000 deliveries a year.

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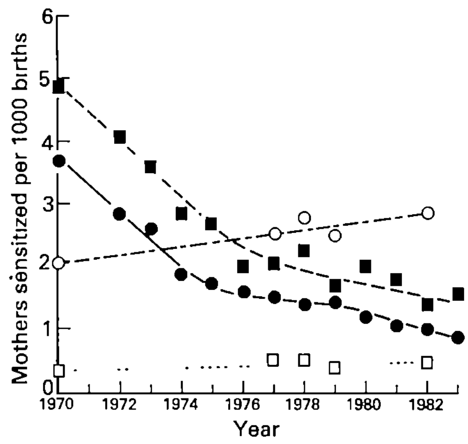

Fig. 1. Incidence of pregnancy blood group sensitization per 1000 births. Anti-D sensitization: (●——●) new cases; (■——■) old cases Other than anti-D sensitization: (○——○) Rh D positive women; (□——□) Rh D negative women.

New cases of anti-D sensitization, 1980–1983

During this 4-year period 438 women were delivered with anti-D antibodies in their sera, 163 were new cases in that they had developed anti-D antibodies after the introduction of postpartum Rh prophylaxis. They can be divided into four groups (Table 1).

Group (1). Failures of administration

These are women who, although eligible for anti-D prophylaxis, did not receive an injection. During the four 4 years of the survey, 36 women who had failed to receive anti-D immunoglobulin after a previous pregnancy or abortion, although eligible, were found to have anti-D antibodies in their sera in the next pregnancy; 50% followed failure of administration after abortion, the remainder after normal delivery or a stillbirth (Table 1).

Abortions. The 18 cases that occurred following abortion are detailed in Table 2. There are two points of interest. First, nine of the 18 (50%) cases followed induced abortions and antibodies were detected at ≤30 weeks gestation in the subsequent pregnancy in five of them. One woman had a hydropic stillbirth and three others had infants requiring exchange transfusion. If one assumed the hydropic infant had a cord haemoglobin (Hb) of 5 g/dl, then the average cord Hb of these five infants was 12·2 g/dl. Second, only one of the other nine women, who had spontaneous abortions, had antibodies detected at ≤30 weeks in the next pregnancy. No child was severely affected and only one required an exchange transfusion. The average cord Hb level was 15·5 g/dl. Thus women having a surgical termination of pregnancy not covered by anti-D prophylaxis showed a greater degree of Rh immunization than those having a spontaneous abortion.

Normal deliveries or stillbirths. Eighteen women were found to have antibodies in a subsequent pregnancy having failed to receive an injection of anti-D after the previous normal delivery or stillbirth. An 'explanation' for the failure of administration was possible in 11 of them. Three had stillbirths, one was delivered in Bangladesh, one had a blood transfusion at delivery, one was a Jehovah's Witness and in another the injection

Table 1. Causes of sensitization in 163 'new' cases of anti-D Rh haemolytic disease, 1980–1983

	1980	1981	1982	1983	Totals	
Total numbers of women sensitized	133	115	96	94	438	
'Old' cases	84	73	55	63	275	
'New' cases	49	42	41	31	163	
Failures of administration						
(a) After full term delivery or stillbirth	8	2	5	3	18	36 (22%)
(b) Abortion	7	3	4	4	18	
Failures of protection	19	21	21	14	75	(46%)
Primigravidae	4	10	6	6	26	(16%)
Previous pregnancy before anti-D available, or previous Rh D negative infant	11	6	5	4	26	(16%)

Table 2. Failure of administration of anti-D globulin after abortion, 1980-1983

			Subsequent pregnancy					
			Antibodies first detected		Cord haemoglobulin (g/dl)			
Type of abortion	Number of women	Length of gestation (weeks)	At ≤30 weeks	At >30 weeks	Range	Mean	Outcome	Requiring ET*
Medically induced	9	8–16	5	4	10 –17·1	12·2	1 Hydrops 8 Live births	3
Spontaneous	9	6–24	1	8	14·1–17·4	15·5	9 Live births	1

*ET, Exchange transfusion.

would appear to have been given to the infant! No cord bloods were tested in three instances and the remaining women had no antenatal care whatsoever. No 'explanation' for the failure of administration was available in the other seven women. An examination of the subsequent pregnancies revealed that of the 14 women delivered of a Rh D positive infant, 11 were so mildly affected that an exchange transfusion was not necessary and three required exchange transfusion. All infants survived.

Thus, in this series of 36 women who failed to receive anti-D immunoglobulin, although eligible, the subsequent Rh D positive infant was more likely to be severely affected if the pregnancy followed an unprotected abortion, particularly a surgical termination.

Group (2). Failures of protection

These are women who received the recommended dosage of anti-D [500 i.u. (100 μg) after full term delivery and 250 i.u. (50 μg) after abortion, and higher doses with a high Kleihauer count] but who, in spite of the injection, developed anti-D antibodies after delivery or in the next Rh D positive pregnancy.

This group contains the largest proportion of new cases, 46% (Table 1). Our previous experience has been that they tend to have mildly affected infants and do not contribute significantly to infant mortality (Tovey & Robinson 1975). This is illustrated in an analysis of the 14 examples of 'failures of protection' in 1983 (Table 3).

Seven of the 14 developed demonstrable antibodies after 30 weeks gestation in the subsequent pregnancy, and all had mildly affected infants, only one requiring exchange transfusion. In the other seven, where antibody was detected before 30 weeks, a similar pattern was observed, six infants were mildly affected and did not require transfusions. The one exception occurred in a woman with a high Kleihauer count after the previous delivery which had necessitated a 5000 i.u. dose of anti-D immunoglobulin. In spite of this, antibody was detected 6 months after delivery and this persisted throughout the next pregnancy rising to 330 i.u. later in the pregnancy. The infant was severely affected and required three exchange transfusions, the cord Hb was 6·6 g/dl.

It is also of interest that 13 of these women had at least two live babies, the one exception being a failure of protection after an abortion. These findings are similar to those reported previously and confirm that in the large majority of cases, women with no antibodies detectable at delivery who receive anti-D immunoglobulin but develop antibodies later are very unlikely to have severely affected infants.

Group (3). Presensitized primigravidae

These are women who had demonstrable anti-D antibodies during their first pregnancy and they represented 16% of all new cases. Their contribution to the morbidity and mortality of Rh haemolytic disease has been described (Tovey & Taverner 1981) and it is this group, we believe, who receive most benefit from antenatal prophylaxis.

Group (4). Previous pregnancies before anti-D immunoglobulin available

The last group in Table 1 consists of those women who became pregnant before anti-D immunoglobulin was available but no antibodies had been detected in these sera at that time. This

Table 3. Details of 14 patients in whom protection failed in 1983

Patient	Obstetric history (ND+M)*	Gestation at first positive antibody test (weeks)	Cord haemoglobin (g/dl)	Exchange transfusions	No. of living children
1	5+0	38	14·2	1	6
2	3+1	40	13·5	No	4
3	3+0	40	15·0	No	4
4	2+1	36	16·8	No	3
5	2+0	36	Not tested	No	2
6	1+0	32	18·0	No	2
7	1+1	40	18·5	No	2
8	1+0	27	17·0	No	2
9	2+0	26	16·6	No	2
10	2+1	20	17·7	No	2
11	1+2	10	14·6	No	2
12	0+1	19	13·1	No	1
13	1+0	20	18·0	No	2
14	1+0	22	6·6	3	2

*ND, Normal delivery; M, Spontaneous abortion. Patient 5 had one cot death.

group will inevitably decrease as a cause of anti-D sensitization.

Infant mortality

In 1970, 66 women lost their infants either before or after delivery because of anti-D antibodies. In 1982 and 1983 there were two instances each year. If one compares this reduction with the decline in numbers sensitized (Table 4) one can see that there has been a 70% reduction in maternal sensitization and exchange transfusion incidence, but a 96% reduction in mortality.

Exchange transfusion rates

A comparison between the numbers of infants who required exchange transfusion in 1970 and those of today shows a reduction from 120 to 25 (Table 4). This means that the large obstetric units will exchange-transfuse only two to four babies a year, and the smaller ones even fewer.

Antibodies other than anti-D

Anti-D prophylaxis, although reducing the occurrence of anti-D haemolytic disease, has had little effect on the occurrence of other blood group antibodies, and today these outnumber anti-D cases (Table 5, Fig. 1). Although it is only on exceptional occasions that these 'rare' antibodies (e.g. anti-Fy^a-s) cause haemolytic disease, women with anti-c and anti-Kell demand close attention.

Of the three stillbirths due to antibodies other than anti-D in this Region during the last few

Table 4. Incidence of anti-D sensitization, infant deaths and exchange transfusion rates

	1970		1982		
	Number	Per 1000 births	Number	Per 1000 births	Fall in incidence
Total mothers sensitized	469	8·6	96	2·4	72%
New cases	202	3·7	41	1·0	73%
Long-standing cases	267	4·9	55	1·4	72%
Infants requiring exchange transfusion	120	2·2	25	0·64	70%
Infant deaths, stillbirths and neonatal deaths	66	1·2	2	0·05	96%

Table 5. The incidence of maternal sensitization to blood antigens other than D*

	D status			
	1970		1982	
Antibody	+ve	−ve	+ve	−ve
Anti-c	25		20	
Anti-c+E	10		10	
Anti-C and/or C^w	9	2	3	—
Anti-e	3	—	1	—
Anti-E	39	8	41	9
Anti-K	15	4	22	5
Anti-Fy^a	4	—	7	1
Anti-S	3	—	—	1
Anti-s	—	—	1	—
Anti-M	2	—	1	—
Anti-Lu^a	1	—	2	—
Anti-Fy^b	—	—	1	—
Others and mixtures	5	1	3	2
Totals	115	15	117	18
Per 1000 births	2·1	0·3	2·9	0·45

*ABO haemolytic disease has also been excluded

years, two have been due to anti-c and one to anti-Kell.

Discussion

Undoubtedly there have been spectacular changes in the occurrence of haemolytic disease of the newborn, the clinical picture, and particularly the management of pregnant women with blood group antibodies.

After a very encouraging drop in the number of women sensitized to the D antigen following the introduction of postpartum anti-D prophylaxis, the impetus has not been maintained and although there are fewer cases each year, the hope in those early days, that Rh haemolytic disease would in a few years become a matter of medical history, has not been fulfilled. Two major obstacles remain, the continuing failure to administer anti-D immunoglobulin to eligible Rh D negative women, and the problem of intra-pregnancy sensitization, rendering postpartum anti-D prophylaxis impotent.

It is not often appreciated that the problem of administrative failures is not confined to full term deliveries, half the cases in the present series followed failures of administration after abortion. Previously the author has expressed the view that the major problem to be overcome was in women having a spontaneous abortion, (Tovey *et al.* 1978), however, a closer analysis of our data revealed that this was incorrect, half of our cases followed induced abortions and, what is perhaps of greater significance, these were more severely sensitized than the cases after spontaneous abortion. The clinical picture in the pregnancy subsequent to an unprotected spontaneous abortion resembled more the clinical picture seen in primigravidae, and lends support to the view that early spontaneous abortion is not a significant cause of maternal sensitization. This is certainly not true of surgical terminations, presumably because of the increased chance of a red cell 'leak' into the maternal circulation. Thus it is even more essential to ensure that all Rh D negative women who have an induced abortion receive a dose of anti-D immunoglobulin.

The circumstances in which some women fail to receive an injection after a full term delivery are still not clear. Some have been delivered in countries with few facilities for Rh prophylaxis and a few have religious reasons for rejecting prophylaxis. Occasionally other more urgent medical problems arise at the time of delivery relegating Rh prophylaxis to the background, but in the majority no reason for the failure of administration can be found. Very recently we sense that the numbers of failures of administration are falling slightly, and are not quite so pessimistic.

Our practice of issuing a special card to each Rh negative patient to remind the obstetrician that the patient is eligible to receive postpartum anti-D, or the addition of this to routine blood grouping cards, may well have resulted in fewer failures of administration, but this is difficult to prove.

There is no doubt that a dramatic reduction in the number of administrative 'failures' will only occur when all obstetricians and midwives take positive measures to ensure that all eligible women receive an injection of anti-D immunoglobulin after delivery.

The analysis of the cases of 'failures of protection' revealed that although half the women developed antibodies after 30 weeks in the subsequent pregnancy and not surprisingly the infants were mildly affected, this also applied to women who were found to have antibodies early in the subsequent pregnancy. Only one infant was severely affected and in this instance the mother had had a large fetal 'bleed' during her previous delivery, and even the administration of a large dose of anti-D immunoglobulin failed to protect. These findings are similar to those reported previously (Tovey & Robinson 1975) in that the infants of women who develop antibodies after delivery, or in the next Rh positive pregnancy after receiving anti-D immunoglobulin after a previous Rh positive pregnancy, are unlikely to be severely affected.

The fact that antibodies were detected after 30 weeks in half these women is relevant to antenatal prophylaxis. Of the 75 women in this 4-year study in whom protection failed, an estimated 38 developed anti-D after 30 weeks in the subsequent Rh positive pregnancy and these might have been protected by antenatal prophylaxis. If one adds to this number the 26 primigravidae who developed anti-D towards the end of their first pregnancy, 64 out of a total of 163 (40%) may well have been protected by antenatal prophylaxis. Arguments against the routine administration of anti-D immunoglobulin antenatally have been entirely concerned with its cost effectiveness and a number of experts have concluded antenatal prophylaxis was not justified on these grounds (Tovey 1980, Nusbacher & Bove 1980). However, a recent and much more detailed cost analysis from Canada concludes that antenatal prophylaxis is cost effective, particularly for primigravidae (Torrance & Zipursky 1984). As more anti-D immunoglobulin becomes available, increasing numbers of obstetricians are adopting the policy of offering Rh negative mothers with no living child a 500 i.u. injection of anti-D immunoglobulin at 28 and 34 weeks gestation.

There have been major changes in the management of pregnant women who have developed anti-D antibodies. Firstly the introduction, particularly in Great Britain, of a more standardized technique for anti-D measurement in pregnancy (Bowell *et al.* 1982) has resulted in obstetricians being prepared to embark on more heroic measures to prevent intrauterine death in the 'high-risk' pregnancy. This includes intensive plasma exchange (Robinson 1984), very premature delivery (Spiedel 1984), intrauterine transfusion (Frigoletto *et al.* 1981; Rodeck *et al.* 1984). One conclusion to be drawn from our study is the great advantage derived from 'regionalizing' maternity services for high-risk mothers with antibodies. In a region of over three million population with 40 000 deliveries a year, and around 100 pregnant women with anti-D antibodies, exchange transfusion is only performed approximately 20 times a year, thus small obstetric units will perform no more than one or two a year. Added to this is the very special expertise necessary for plasma exchange, intrauterine transfusion, and the nursing of very immature infants. There is no doubt that the improved results in this Region are due to a small group of obstetricians, paediatricians, haematologists and blood transfusion personnel backed up by a devoted nursing personnel with unique expertise in this field, who manage the majority of the high-risk cases. Thus between 1970 and 1984 there has been a 96% reduction in infant deaths due to anti-D haemolytic disease but only a 70% reduction in the number of women sensitized. We are more successful in saving the infants than in preventing women becoming sensitized.

Finally, the encouraging reduction in numbers of women with anti-D antibodies in their sera has not affected in any way the incidence of other blood group antibodies, in fact there appears to have been a slight increase. This is likely to be more apparent than real, because of improved techniques for antibody detection. One interesting fact is that the number of Rh D negative mothers who develop other blood group antibodies has not decreased. If, as has been alleged, anti-D immunoglobulin acts in a non-specific way, simply by removing fetal cells, (Woodrow *et al.* 1975), then the introduction of anti-D immunoglobulin should have caused a reduction in the incidence of other antibodies in Rh negative women as well as anti-D, and in our series this has not occurred. Thus anti-D immunoglobulin may protect in a much more specific way, such as the mechanism suggested by Pollack *et al.* (1982) of antibody mediated immune supression (AMIS).

Although women with antenatal sensitization by other than the D antigen now outnumber those with anti-D, they rarely present a major clinical problem. They may cause difficulties in cross-matching and therefore need to be detected and identified. Clinically the only antibodies likely to cause even moderate haemolytic disease of the newborn are anti-c (often plus anti-E) and anti-Kell. Other blood group antigens can provoke an antibody response, but these are of little clinical significance (Table 5).

Only 10% of people are Kell positive, so that most women who have anti-Kell, will not have had a Kell positive infant and will have developed anti-Kell as a result of a previous blood transfusion. Knowledge of the identify of the antibody is important if a blood transfusion is required. However, a Kell positive infant can be severely affected by maternal anti-Kell and the facilities required for women with anti-D antibodies should be available. Anti-E alone is usually a 'naturally occurring' IgM antibody and is unlikely to cause haemolysis in the fetus.

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A randomized trial of Citanest with Octapressin for relief of pain associated with laser vaporization of the cervix

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Summary. Fifty women undergoing laser vaporization of the cervix for cervical intraepithelial neoplasia were randomly allocated to one of two groups. In one group the patients received no anaesthesia, in the other the ectocervix was infiltrated with 2 ml of Citanest with Octapressin (prilocaine 3% with 0·03 i.u./ml. of felypressin) immediately before the procedure. The pain experienced by each group was assessed immediately after treatment by visual analogue and verbal rating scales. The pain experienced by those women receiving local anaesthesia was significantly reduced as assessed by the visual analogue scale ($P = 0{\cdot}011$) and this reduction was not quite significant by the verbal rating scale ($P = 0{\cdot}06$). The Citanest group had less troublesome bleeding but the difference in bleeding between the two groups was not significant.

Carbon dioxide laser surgery has emerged as an effective method for the destruction of cervical intraepithelial neoplasia (CIN). Common practice in the United Kingdom is to perform laser vaporization for treatment of CIN without any form of analgesia or anaesthesia. Few objective studies have been performed to assess the degree of pain experienced. It has been reported that 40% of patients experience significant discomfort as assessed by a verbal rating scale (Jordan & Mylotte 1981). It is thought that a visual analogue scale reflects more accurately pain experienced during operative procedures (Huskisson 1983). This has been shown to be useful in the assessment of pain experienced in other out-patient gynaecological procedures (Siddle *et al.* 1983). A four point verbal scale was also used.

The nerve supply of the cervix is unclear, but the richest supply appears to be at the level of the internal os and the ectocervix appears to be relatively insensitive to extremes of temperature with few specialized nerve fibres (Jordan & Singer 1976). Local anaesthetic of 1% lidocaine injected into the cervix has been used successfully in the relief of pain associated with laser vaporization of the cervix; however, infiltration with the local anaesthetic itself was uncomfortable and nearly always caused bleeding and thus the length of the whole procedure was considerably increased (Anderson 1982). Routine use of paracervical block using 1% lidocaine with adrenaline providing good anaesthesia and minimizing blood loss, has also been reported (Stanhope 1983), but this is a relatively more difficult technique than local infiltration. Since surgical procedures should be made as pain-free as possible, this study was planned to test the value of local infiltration with Citanest plus Octapressin a combination which has been used for many years in dentistry to provide effective

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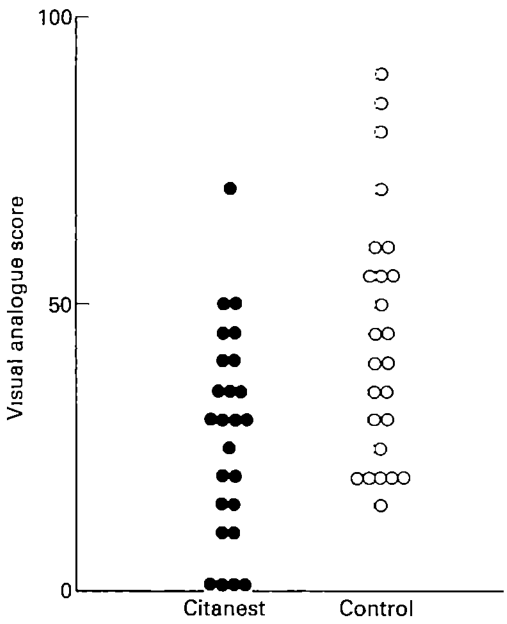

Fig. 1. Visual analogue scores for pain associated with laser vaporization of the cervix recorded on completion of the procedure. 0, 'no pain at all', 100, 'pain as much as you can imagine.' (●) Citanest; (○) control

local anaesthesia combined with reduction in blood loss.

Patients and methods

The study was a randomized comparison of two groups of 25 patients each undergoing laser vaporization for CIN. All patients were premenopausal and aged between 19 and 39 years. One group received local infiltration with Citanest with Octapressin, the other group no anaesthesia or analgesia. All patients gave verbal consent following a description of the technique and the nature of the trial. The level of anxiety before the procedure was measured before the patient undressed using the Spielberger state anxiety inventory (Spielberger *et al.* 1970). The patient was then placed in a colposcopy chair and a colposcopic examination was performed. A Coherent System 450 carbon dioxide laser with a power density setting of 30 W/cm^2 was used with a spot size of 1·8 mm. The vaporization was performed by the same operator in all patients to minimize variations in technique. The whole of the transformation zone was destroyed to a depth of 7 mm and the diameter of the resulting crater measured. The bleeding was assessed on a four point scale ranging from none to troublesome. The time required for the completion of the laser vaporization was recorded. Patients in the Citanest group were given 2 ml of 3% Citanest with Octapressin (prilocaine hydrochloride 30 mg/ml, felypressin 0·03 i.u./ml) using a 30 gauge dental needle on a dental syringe. Infiltration around the periphery of the transformation zone was performed immediately before the procedure. Local anaesthetic was employed in the control group only when significant pain was experienced. The severity of the pain was assessed at the end of the procedure using visual analogue and verbal rating scales. Pain relief after the administration of Citanest with Octapressin in the control group was also assessed using a verbal rating scale. The visual analogue scale consisted of a 100 mm line drawn on plain paper representing pain ranging from 'no pain at all' to 'pain as much as you can imagine' Patients marked a point on the line at the end of the procedure which they felt corresponded to the pain they experienced. The verbal rating scale consisted of a choice of four descriptions, none, mild, moderate or severe. The results from the verbal rating scale and the visual analogue scale were compared using the Mann–Whitney *U*-test. The patients were also asked whether they had experienced sweating, nausea, dizziness or abdominal cramps. Both groups of patients were also asked if they were willing to undergo the treatment again.

Table 1. Verbal rating scores for pain associated with laser vaporization recorded on completion of the procedure

Pain score	Citanest (n = 25)	Control (n = 25)
None	5	—
Mild	9	10
Moderate	11	11
Severe	—	4

Results

Pain

The pain experienced by the group receiving Citanest with Octapressin was statistically significantly less as assessed by the visual analogue scale (P = 0·011) (Fig. 1), and not quite significant by the verbal rating scale (P = 0·06) (Table 1). Seven patients in the control group had suffi-

Table 2. Rating score for bleeding associated with laser varporization of the cervix

Bleeding score	Citanest ($n = 25$)	Control ($n = 25$)
None	19	14
Slight	2	3
Moderate	2	3
Troublesome	2	5

cient pain to require local anaesthesia to complete the treatment, and of the seven patients, four had complete pain relief and the remainder described the pain relief as moderate. No patient in the Citanest group requested cessation of treatment because of pain and all patients in the group were prepared to undergo treatment again. Only 16 patients in the control group were prepared to undergo the procedure without local anaesthesia if available. There was no significant difference in the anxiety score between the two groups ($P = 0{\cdot}3$) nor was there any relation between the anxiety score and the pain experienced in either group.

Time required to complete treatment

The resultant crater was of comparable size in the two groups (mean diameters were 18·6 mm in Citanest group and 18·3 mm in control group). The mean time for the completion of laser vaporization was 9·6 min (SEM 1·7) in the Citanest group and 15·1 min (SEM 1·7) in the control group ($P<0{\cdot}05$).

Bleeding

Troublesome bleeding sufficient to interfere with the procedure was not common in either group, but was apparent in seven patients, five in the control group and two in the Citanest group. The blood loss was not measured and was a subjective impression by the operator (Table 2).

Other side-effects

Except for sweating in four patients (16%) no other untoward effects were noted in the Citanest group. In the control group, 14 patients (56%) had sweating, seven (28%) had abdominal cramps and three (12%) had dizziness during laser vaporization. There were no consistent side-effects that could be attributed to prilocaine.

Discussion

The use of local anaesthesia before laser vaporization has in the past been associated with troublesome bleeding (Anderson 1982). This problem appears to be overcome with the use of Citanest with Octapressin given through a fine gauge dental needle. The blood loss is reduced to an acceptable level if not to a level less than that usually encountered. The overall time of the procedure is also reduced. Although not a double-blind control trial, which would have eliminated observer bias or placebo effect, there was evidence to suggest a good analgesic effect. The purpose here was to compare a new method of achieving analgesia with current practice. A larger double-blind trial would be necessary to confirm our findings. The authors have made this technique routine in their clinic

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The use of the fasciocutaneous flap in vaginal reconstruction

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Summary. Vaginoplasty in two girls with severe vaginal stricturing due to congenital adrenal hyperplasia is described. The strictures were so tight and long that conventional flap techniques were inappropriate, and long fasciocutaneous flaps from redundant labioscrotal tissue were used. This technique has gained wide usage in plastic surgery, but has not been described previously in this site.

Congenital adrenal hyperplasia is the commonest cause of masculinization in the female newborn. Clitoromegaly and labial fusion are usually noted at birth and the diagnosis made by appropriate biochemical investigation. Clitoral reduction is commonly performed in the neonatal period or early infancy and further vulvovaginal surgery deferred until the child is fully grown.

The vagina is always present in these patients, and the internal genitalia are normal. However, the degree of masculinization of the external genitalia is variable, ranging from thin fused labia, merely obscuring a normal vagina, to severe stenosis of the distal two thirds of the vagina, with a single urogenital sinus and large labioscrotal folds (Fay 1974).

We describe two patients in whom long fasciocutaneous flaps were taken from redundant labioscrotal folds and used to enlarge the vagina along almost its entire length.

Patients and methods

The first patient was born with ambiguous genitalia. A diagnosis of salt-losing, 21-hydroxylase deficiency adrenogenital syndrome was made, and she has been maintained on cortisone acetate, 25 mg, and fludrocortisone, 0·2 mg, daily ever since. A deep clitoral amputation was performed soon after birth and no further action taken until puberty at 11 years of age. At that time, it was clear that further vaginal surgery would be necessary but it was thought advisable to defer this until the patient was more emotionally mature and fully grown.

Aged 17 years, the patient was menstruating regularly and had well-developed secondary sexual characteristics. Examination under anaesthesia revealed bilateral erectile tissue on either side of a single urogenital sinus. The external urethral orifice was identified and the bladder emptied. The thick mid-line raphe was divided posteriorly in the mid-line to reveal a tiny introitus. Dilatation was attempted but could not proceed beyond Hegar 10. Figure 1 indicates the abnormality found. It was decided that a two stage procedure should be undertaken. Firstly, the introitus was enlarged by a posterior midline incision with transverse suturing. This healed well.

Six months later, a definitive vaginoplasty was performed. The findings were as previously described: a normal length, very narrow vagina. There was considerable redundant skin in the labioscrotal folds and it was decided that a fasciocutaneous flap should be raised from this tissue. The vaginal wall was incised posteriorly to above the proximal extent of the stricture only 1–2 cm from the cervix. This relieving incision produced a normal calibre vagina with a mucosal

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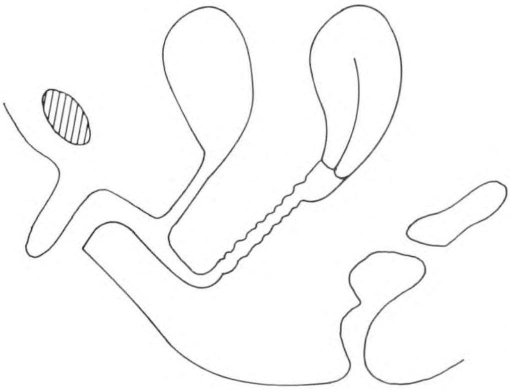

Fig. 1. Diagramatic representation of the severe external genitalia masculinization and vaginal narrowing found in the two patients.

defect approximately one third of its circumference and greater than four fifths of its length. The fascial tissue under the intended flap was infiltrated with 20 ml of 1:100 000 adrenaline in normal saline solution. The flap was based posteriorly and required to be not less than 9 cm in length by 3·5 cm in width. To ensure an adequate blood supply to the distal end of the flap, the incision was carried down to the deep fascia, thus raising a large bulk of adipose tissue and bulbocavernosus tissue attached to the skin. The flap was then transposed through 75° to fill the mucosal defect in the vagina, and sutured to the defect edges with interrupted chromic catgut stitches (Figs 2–5).

The postoperative course was uncomplicated. On the fourth day a discharge was noted and vaginal irrigation with hydrogen peroxide solution was started. Vaginal swabs were negative. The patient was discharged 7 days postoperatively. Vaginal dilatation was judged unnecessary.

When reviewed last, 8 months postoperatively, the vagina was of normal diameter, with the cervix clearly palpable. The bulky subcutaneous adipose tissue which had been raised with the flap had disappeared. The hair growth on the skin flap was remarkably sparse. There was a small dog-ear fold of skin on the perineum (the base of the transposed flap) and the redundant labioscrotal fold on the right side remained. The patient was, however, happy with the cosmetic result and wished no further operation. She has not yet attempted intercourse, but inserts tampons easily.

The second patient presented at 11 days of age with vomiting and a diagnosis of salt-losing 21-hydroxylase deficiency was made. Her maintenance therapy is dexamethosone, 0·75 mg, and fludrocortisone, 0·5 mg, daily.

Ambiguous genitalia in the form of an enlarged clitoris, single urogenital sinus, fused labia and rugose labioscrotal folds were noted at birth, but no surgery undertaken until 2 years of age. At that time, a clitoridectomy was performed.

At 12 years of age, before the onset of menstruation, she was examined under anaesthesia to determine whether any procedure to enlarge the vagina would be necessary. A single urogenital sinus was probed and the urethra identified. Despite division of the fused labia, the vaginal orifice was not identified.

The patient was referred to the Chelsea Hospital for Women, London, at the age of 13 years. She was an emotionally and developmentally immature girl and had not yet had a period. It was decided that further examination and surgery would be deferred until she was 16 years old.

At 16 years of age, she was admitted for sur-

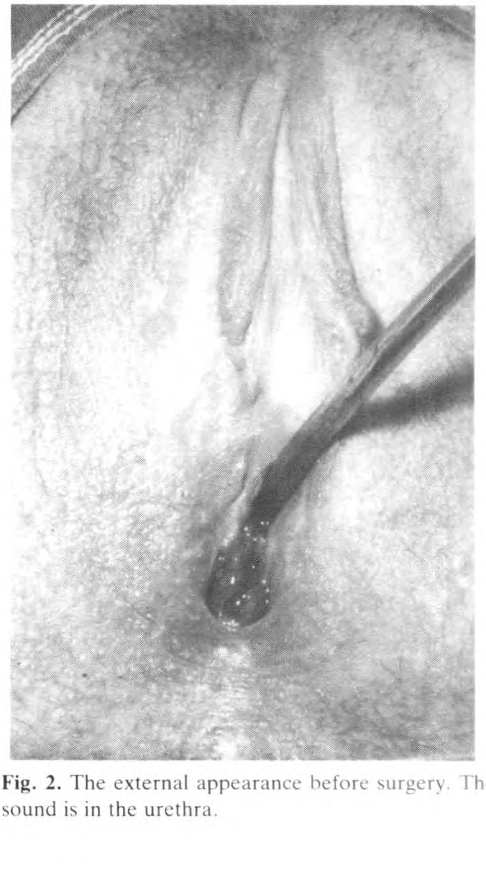

Fig. 2. The external appearance before surgery. The sound is in the urethra.

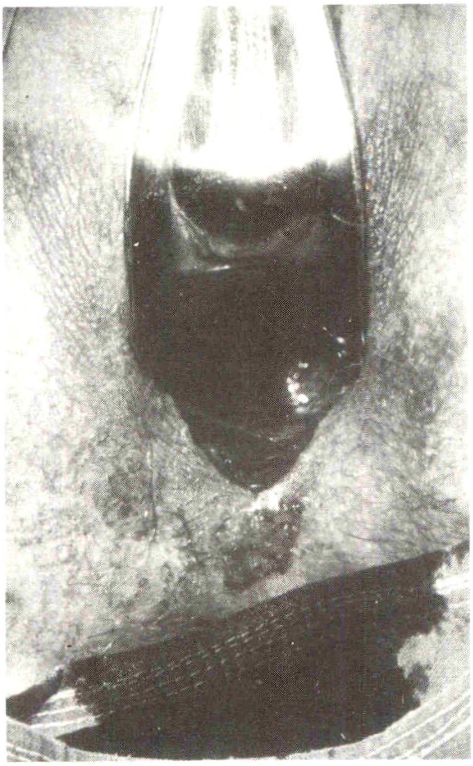

Fig. 3. The perineum has been divided posteriorly and the incision carried almost to the vaginal vault revealing abnormal calibre vagina into which a Sim's speculum has been inserted anteriorly.

gery. She was still amenorrhoeic, but breast and pubic hair development were well advanced. Examination under anaesthesia showed a large amount of erectile tissue encircling the vagina. A single 0·5 cm diameter orifice was identified in the vulva and after dilatation of this orifice, it was possible to identify the vagina, separate from the urethra. The vagina was, as expected, of normal length. The abnormality found is indicated in Fig. 1. It was decided that a two-stage procedure should be undertaken and an initial flap introitoplasty was performed immediately. An inverted V-shaped incision was made in the perineum, and a superficial flap, of 4 cm in length and 3 cm base, raised. A 3 cm mid-line incision was made in the posterior vaginal wall and the apex of the triangular flap was sutured to the apex of the vaginal incision. The postoperative course was uncomplicated and the flap healed well.

Two months postoperatively, the introitus would admit a finger tip only and vaginal dilatation was commenced by the patient, using a number one perspex dilator. Depite this, the introitus continued to narrow and it was decided that the definitive fasciocutaneous flap should be undertaken immediately. This was performed using the technique described in the first patient. The postoperative period was uncomplicated. The vagina was irrigated with hydrogen peroxide solution from 3 days after the operation and the flap healed well. Dilators were not considered necessary and she was discharged from hospital 7 days after the operation.

When last reviewed, 9 months postoperatively, she was still amenorrhoeic, despite different hormone replacement therapy. The vagina was well healed and remarkably the upper vagina was relatively hair free. It was of good dimensions, admitting two fingers easily, with the cervix clearly palpable. Intercourse had not been attempted. The cosmetic appearance was satisfactory, with a perineal dog-ear of skin. Again, the patient was happy with the result and wished not further action.

Discussion

These two patients represent a severe form of congenital adrenal hyperplasia with marked

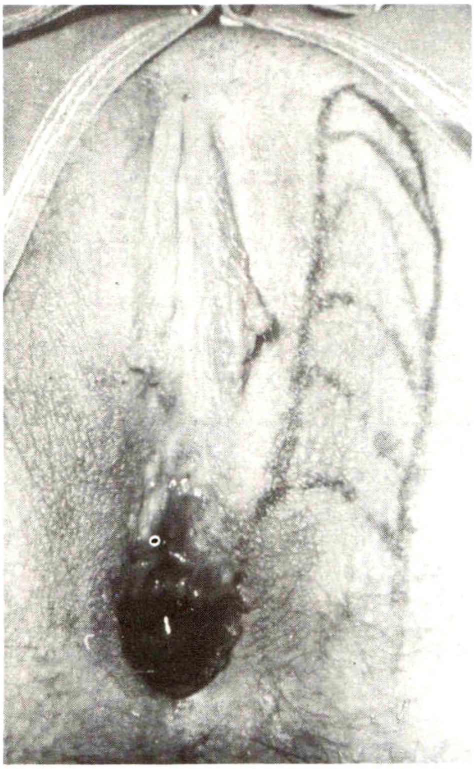

Fig. 4. Flap outlined on the vulval skin.

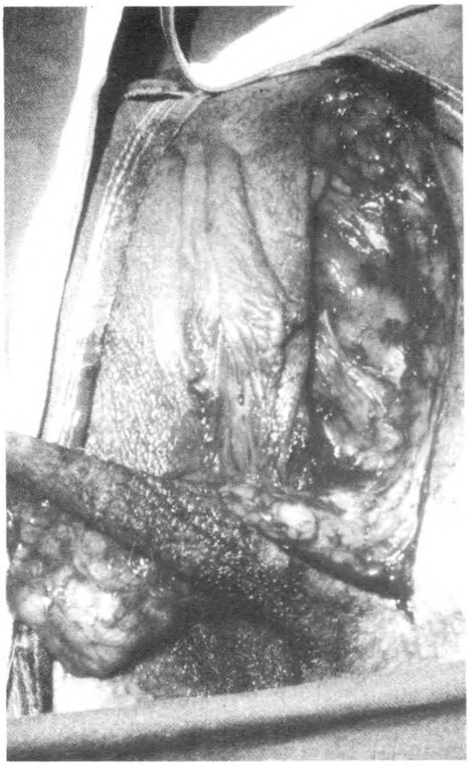

Fig. 5. The flap has been turned down before being folded into the vaginal defect. Note the large amount of fat and other deep tissue attached beneath the skin of the flap.

masculinization and vaginal narrowing. They may, nevertheless, anticipate fertility as well as normal coital activity. The use of fasciocutaneous flaps has become popular in plastic surgery, as a method of increasing the area of viable skin which can be transposed as a pedicle flap graft (Cormack & Lamberty 1984). This is the first report of the use of this technique for vaginal enlargement. In techniques described previously (Dewhurst & Gordon 1969) more superficial triangular flaps of skin with little subcutaneous tissue have been used but with this technique, the length of the flap from base to apex cannot be greater than one and a half times the width of the base, or viability of the apex of the flap may be lost. By using the deeper fasciocutaneous flap technique, a good blood supply to the distal part of the flap is ensured, permitting a long flap to be raised which is three times the width of the base. Thus the vagina may be enlarged throughout its length, even when narrowing is present high up, near the cervix.

This is particularly useful in the clinical situation of severely masculinized patients as the large labioscrotal folds provide abundant skin and indeed the appearance of the labia is improved by the removal of redundant tissue. In each patient a unilateral flap was used but in more severe cases or in case of flap failure, the other side is also available.

This technique has been used successfully on two further patients in the same clinical circumstances since the original preparation of this paper.

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Primary and myoma-associated menorrhagia: role of prostaglandins and effects of ibuprofen

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Summary. The release of 6-keto-prostaglandin $F_{1\alpha}$(6-keto-$PGF_{1\alpha}$), a metabolite of prostacyclin (PGI_2) and thromboxane B2 (TxB2), a metabolite of thromboxane A2 (TxA2), was estimated in endometrial biopsies taken from 12 menorrhagic and 12 healthy women during the luteal phase of the cycle. The releases of 6-keto-$PGF_{1\alpha}$ and TxB2 were normal, but the ratio TxB2/6-keto-$PGF_{1\alpha}$ was inversely related to menstrual blood loss in women with measured menstrual blood loss exceeding 70 ml. In the second part of the study, 24 women with excessive menstrual bleeding (13 with primary menorrhagia, 10 with uterine fibromyomas, one with haemostatic factor VIII deficiency) were treated at random with ibuprofen (600 mg/day and 1200 mg/day) and with a placebo. Ibuprofen 1200 mg/day reduced ($P<0{\cdot}01$) median blood loss from 146 ml (range 71–374 ml) to 110 ml (30–288 ml) in primary menorrhagia but had no effect on blood loss in women with uterine fibroids and factor VIII deficiency. Blood loss was normal in six women and was not affected by ibuprofen. Thus, our data suggest that there is a PGI_2 dominance in the endometrium of patients with menorrhagia. In addition, primary, but neither fibromyoma nor coagulation defect-associated menorrhagia, can be treated by ibuprofen.

The endometrial uptake of arachidonic acid, an essential precursor for prostanoid biosynthesis, is increased (Downing *et al.* 1983) and conversion of exogenous arachidonic acid to prostaglandin E_2 (PGE_2) (Smith *et al.* 1981*a*) and prostacyclin (PGI_2) (Smith *et al.* 1981*b*) is enhanced in menorrhagic endometrium. PGE_2 and/or PGI_2 are vasodilatory and antiaggregatory agents and could account for the increased menstrual blood loss. However, the endometrium also produces the vasoconstrictory and proaggregatory thromboxane A2 (TxA2) (Liggins *et al.* 1980), but its relation to menorrhagia has not been studied. The role of prostanoids in primary menorrhagia gains further support from the reductions in menstrual blood loss during the use of cyclo-oxygenase inhibitors (Anderson *et al.* 1976; Haynes *et al.* 1980; Fraser *et al.* 1981). Clinically, however, uterine fibromyomas are frequently associated with menorrhagia, but no data exist on the effect of cyclo-oxygenase inhibitors on myoma-associated menorrhagia. The present study was conducted to explore the release of PGI_2 and TxA2 by menorrhagic endometrium and to compare the effect of ibuprofen, a well-known cyclo-oxygenase inhibitor, on primary and myoma-associated menorrhagia.

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Patients and methods

Thirty women complaining of excessive menstrual bleeding volunteered for this trial (Table

Table 1. Clinical characteristics of the study population

	Number	Age (years) Mean (range)	Subsequent hysterectomy
Menorrhagia*			
Primary	13	39·2 (29–48)	4
Myoma-associated	10	44·6 (39–49)	7
Factor VIII deficiency	1	49	—
Normal blood loss†	6	35·5 (30–44)	—
Control women	12	36·3 (28–46)	—

* Menstrual blood loss >70 ml

† Menstrual blood loss ≤70 ml.

1). Otherwise they were healthy and had used no drugs or intrauterine contraception within 3 months preceding or during the study. Thirteen women had uterine fibromyomas, assessed by pelvic examination, ultrasonography, or by examination of the uterus in the seven women who subsequently underwent hysterectomy; 10 of the women with fibroids were menorrhagic. The uterus appeared to be normal in 17 women, and this was confirmed in four at subsequent hysterectomy. Fourteen of these women were menorrhagic; one due to deficiency of haemostatic factor VIII (27–45% of the normal); whereas three women lost less than 70 ml. Thus 13 women had primary menorrhagia.

Endometrial biopsies were taken from 12 menorrhagic women (6 with primary menorrhagia, 6 with fibromyomas) and from 12 healthy control women between the menstrual cycle days 21 to 24. These biopsies were taken from menorrhagic women after ibuprofen-placebo comparison was completed and thus some 3 weeks after the last ibuprofen or placebo tablet. The endometrial specimens were washed free from blood and immediately frozen at −70°C until used for assessment of PGI$_2$ and TxA2 release. Briefly, appropriate samples (10–20 mg dry weight) were perfused with Eagle's medium at 37°C, pH 7·4, CO$_2$/O$_2$ 5%/95%. To eliminate the effect of trauma the specimens were first perfused for 2·5 h (washout period), and then a 1-h fraction was collected and assayed for 6-keto-PGF$_{1\alpha}$, a metabolite of PGI$_2$, and TxB2, a metabolite of TxA2 (Makilä *et al.* 1983). To this end, the samples were acidified to pH 3·0 with HCl (0·1 mol/l) and extracted twice with twofold excess of ethylacetate. The combined supernatants were evaporated to dryness under a nitrogen stream and redissolved in buffer, out of which samples were taken in duplicate for saturation analysis employing specific antibodies, as described previously (Mäkilä *et al.* 1982). Indomethacin (5x10^{-5} mol/l) inhibited the releases of 6-keto-PGF$_{1\alpha}$ and TxB2 in this system. The results are expressed in ng of prostanoid/g of dry weight tissue per 1 min. Due to the small amount of endometrial material, we could not check if the storage of the sample in the frozen state had any effect on the endometrial prostanoid release but, judging from previous data on the prostanoid release by the umbilical vessels, storage has no effect on the capacity of tissue to produce PGI$_2$ and TxA2 in this system (Mäkila *et al.* 1982).

The 30 women were treated with ibuprofen 600 mg daily, 1200 mg daily, and with a placebo (composed of potato starch, lactose, magnesium stearate and gelatin), each during one cycle, in a randomized, double-blind manner during three consecutive menstruations. The order of the treatments was randomized by the manufacturer using tables for random numbers. The women were advised to start the treatment (one tablet three times a day) at the beginning of menstrual bleeding and to continue it to the end of bleeding or for a maximum of 10 days; a check was kept by counting the remaining tablets after each course of treatment. After the first 3-month study period, seven women discontinued but 23 continued the trial and used 600 mg/day of ibuprofen, 1200 mg/day of ibuprofen and a placebo in randomized order during the following three menstruations. Thus in 23 women two menstruations were studied during each treatment, whereas in seven women only one menstruation during each treatment could be evaluated. The sanitary pads and tampons collected into consecutively numbered polyethylene bags were eluted with 5% NaOH for 24 h, and menstrual blood loss was assessed photometrically as alkaline haematin (Hallberg & Nilsson 1964). The recovery of known amounts of blood (5–25 ml, $n = 10$) placed on the pads and tampons ranged between 94 and 102%. In addition, the women filled in questionnaires on the duration of menstrual bleeding, menstrual pain, the number of tablets used, side-effects, and additional medication.

Statistical methods

The Wilcoxon test for paired and unpaired samples and Kendall's rank correlation test were used to assess the significance of the differences.

Results

Endometrial release of 6-keto-PGF$_{1\alpha}$ and TxB2

All endometrial specimens released more TxB2 (range 8·39–59·92 ng/g/min) than 6-keto-PGF$_{1\alpha}$ (range 1·06–6·75 ng/g/min) but there was no significant difference between menorrhagic and healthy women in this regard (Table 2). Furthermore, neither 6-keto-PGF$_{1\alpha}$ nor TxB2 release was related to blood loss in menorrhagic women. The ratio of TxB2 to 6-keto-PGF$_{1\alpha}$ release was not significantly different in primary or myoma-associated menorrhagia or in the controls (Table 2) but it was, however, inversely related to menstrual blood loss ($n = 12$, $r = 0{\cdot}50$, $P<0{\cdot}05$).

Effects of ibuprofen

Ibuprofen treatment at 1200 mg/day decreased the median blood loss by 25% ($P<0{\cdot}01$) in primary menorrhagia, but had no effect on blood loss in patients with uterine fibroids, factor VIII deficiency, or in women with normal blood loss (Table 3). Blood loss was decreased in all but one woman with primary menorrhagia (Fig. 1) and this decrease was relative to blood loss without active treatment ($n = 13$, $r = 0{\cdot}79$, $P<0{\cdot}01$). Ibuprofen, 600 mg daily, did not significantly reduce blood loss in any of the groups (Table 3; Fig. 1). Ibuprofen treatment had no effect on the duration of menstrual bleeding in any study group (data not shown).

Side-effects

Side-effects were reported by six women during seven placebo cycles (headache, dizziness, nausea, diarrhoea), by six women during seven

Table 2. Endometrial prostacyclin and thromboxane A2 production (as measured by 6-keto-PGF$_{1\alpha}$ and TxB2 release, respectively in a superfusion model) in women with menorrhagia and in healthy controls (ng/g/min; median, range)

	N	TxB2	6-keto-PGF$_{1\alpha}$	TxB2/6-keto-PGF$_{1\alpha}$
Menorrhagia*				
Primary	6	23·60 (15·74–37·82)	3·05 (1·96–5·37)	8·27 (4·98–12·11)
Myoma-associated	6	37·75 (13·37–52·45)	2·72 (1·06–5·25)	13·08 (9·37–18·67)
Controls	12	28·66 (8·89–59·92)	3·25 (1·34–6·75)	8·78 (4·46–17·99)

N, Number of women; * menstrual blood loss >70 ml.

Table 3. The effect of ibuprofen on menstrual blood loss (MBL) (ml; median, range) in primary and fibromyoma-associated menorrhagia and in the patient with factor VIII deficiency

			Ibuprofen	
	N (n)	Placebo	600 mg/day	1200 mg/day
Menorrhagia*				
Primary	13 (23)	146 (71–374)	123 (23–319)	110 (30–288)†
Myoma-associated	10 (17)	138 (71–380)	128 (86–280)	123 (68–374)
Factor VIII deficiency	1 (2)	160	153	171
Normal MBL	6 (11)	37 (11–56)	39 (17–61)	35 (10–56)

N, Number of women; (n), number of menstruations with each treatment

* Menstrual blood loss >70 ml; † $P<0{\cdot}01$ as compared to placebo treatment.

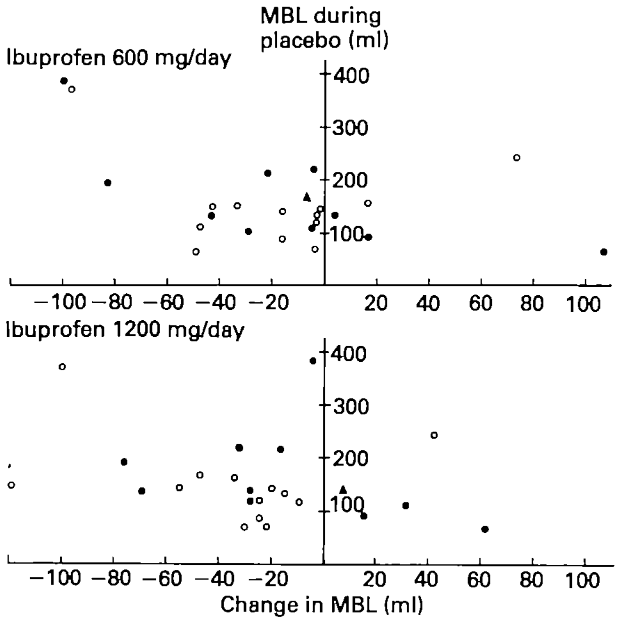

Fig. 1. Change in menstrual blood loss (MBL) during ibuprofen treatment (600 mg/day and 1200 mg/day) (mean of two menstruations in 18 women, one menstruation in six women) in relation to the MBL during placebo use (mean of two menstruations in 18 women, one menstruation in six women) in primary (○), fibromyoma- (●) or factor VIII deficiency-associated (▲) menorrhagia.

cycles with ibuprofen at 600 mg/day (nausea, dizziness, headache), and by five women during ibuprofen at 1200 mg/day (headache, dyspepsia, nausea, diarrhoea). All side-effects were mild and did not result in the discontinuation of the treatment.

Discussion

We studied PGI_2 release in the luteal phase endometrium from endogenous arachidonic acid in a tissue superfusion method and found it to be similar in menorrhagic and healthy women. This finding seems to be in disagreement with increased PGI_2 production by metrorrhagic endomyometrium from exogenous arachidonic acid (Smith *et al* 1981*b*) but nicely in accordance with recent findings of Rees *et al.* (1984*a*) who used similar methods to ours. Prostacyclin synthesis, starting from endogenous arachidonic acid, as in our study and in the work of others, may reflect the inherent PGI_2 synthesis more reliably than PGI_2 synthesis starting from exogenous arachidonic acid. The data from luteal phase endometrium do not necessarily illustrate, however, the situation during menstruation, when the increased content of arachidonic acid in the endometrium (Downing *et al.* 1983) may lead to excessive production of prostanoids (Rees *et al.* 1984*b*), including PGI_2. This could result in menorrhagia.

In theory, menorrhagia could also be caused by a decreased release of proaggregatory, vasoconstrictory TxA2 which functions as an endogenous antagonist of PGI_2. We present evidence that this might be the case: although both PGI_2 and TxA2 productions were normal in menorrhagic endometrium, the balance between TxA2 and PGI_2 shifted to a relative TxA2 deficiency and was negatively related to blood loss in patients with menorrhagia.

Ibuprofen, 1600 mg/day, decreased excessive menstrual bleeding by 32% in IUCD users (Roy & Shaw 1981). It is clear from our present data that ibuprofen also alleviates primary menorrhagia in a dose-dependent manner, the effect being significant at a dose level of 1200 mg/day. These data further support the concept that prostanoids play a role in primary menorrhagia. Being a cyclo-oxygenase inhibitor, ibuprofen should non-selectively suppress the production of both bleeding-promoting and opposing prostanoids. This is, however, not necessarily true with regard to the uterine prostanoids (Powell & Chan 1984) and this may account for the reduced loss that occurs with the use of PG-synthesis inhibitors.

Uterine fibromyomas are commonly associated with menorrhagia. It is not known how fibromyomas cause menorrhagia, but our data suggest that endometrial PGI_2 and TxA2 are of no or minimal importance in this regard. Moreover, ibuprofen failed to reduce the myoma-associated menorrhagia. Thus, uterine factors other than prostanoids, perhaps such as increased fibrinolytic activity (Rybo 1966), may be more important in fibroid-associated menorrhagia. Our data convey an important message to clinicians: fibromyomas should be excluded as a cause for menorrhagia before ibuprofen is prescribed for its treatment.

Acknowledgments

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Menstrual dysfunction in Nigerian athletes

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Summary. Menstrual function was assessed in 475 Nigerian athletes in different sports and 606 non-athletes. In general, irregular menstrual cycles and oligomenorrhoea or secondary amenorrhoea (O/A) were more common in the athletes (26% and 21%, respectively) than in the non-athletes (18% and 8%, respectively). Menstruation was more regular and normal in the non-athletes (50%) than in the athletes (22%). It was noted that menstrual dysfunction in the athletes was associated with significantly low body fat, body weight, relative weight for height, and the stress of sports activity. In the groups of athletes the ball game players (35%) and distance runners (51%) most commonly experienced O/A, whereas the incidence of dysmenorrhoea and menorrhagia was most prevalent in the swimmers (37%), and sprinters (42%). Menstrual disturbances were relatively more common in athletes who began training before the menarche (43%).

Athletic competition for women has increased considerably in recent years. With the renewed interest in women's sports, there has been an increased awareness that regular participation in strenuous exercise can affect female reproductive function (Jools 1984). Results of several studies (Dale *et al.* 1979; Shangold *et al.* 1979; Speroff & Redwine 1980; Baker 1981) have indicated that athletes in endurance sports are more susceptible to menstrual disturbances during intensive training. According to Carlberg *et al.* (1983) estimates from research studies for the incidence of amenorrhoea and other menstrual disturbances among athletes have ranged from 2% to 51%. In contrast, these authors noted that the occurrence of amenorrhoea in non-athletic populations has been estimated at between 2% and 5%. In an earlier study, Malina *et al.* (1978) reported a 28·6% prevalence of menstrual irregularity in a cross-section of college athletes as compared with 22% for non-athletic controls.

Although considerable research evidence suggests that athletic women experience menstrual disorders more frequently than their non-athletic counterparts, there is probably no single factor which could be isolated as accounting for the changes in menstrual function. Consequently, recent investigative emphasis has focused on a multiplicity of factors, ranging from endocrinological profiles (Bonen *et al.* 1981; Shangold 1982), anxiety and emotional stress (Schwartz *et al.* 1981), to body fat and weight (Sogbanmu & Aregbesola 1979; Erdelyi 1980), and physical training (Webb & Proctor 1983). Despite the numerous studies which have been undertaken on the menstrual function of athletes, few have examined different categories of athletes and non-athletes, and it is difficult to compare the results of several earlier studies because of the wide variations in definitions for various menstrual disorders.

This study was undertaken to assess menstrual function in Nigerian athletes of different sports and describe the physical characteristics associated with athletes who experience menstrual

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disturbances. An assessment of athletes' menstrual function provides insight into the influence of physical activity on the female athlete and has implications for designing female athletics programmes.

Subjects and methods

The subjects of this study were 525 athletes and 689 non-athletes drawn from various states of Nigeria. The athletes who were recruited during team practices, sport camps, sport competitions and school classes had at least three years of national level competitive sports experience. The non-athletes were selected from a cross-section of women attending secondary schools, colleges of education and universities in the same localities from where the athletes were recruited.

From the total number of subjects recruited, nine (2%) athletes and 21 (3%) non-athletes were excluded because they were unwilling to provide information on their menarchal age and menstrual characteristics. Furthermore, the data of 41 (8%) athletes and 62 (9%) non-athletes were excluded from the analysis because they were uncertain about their menstrual characteristics, and had, during the previous year, used oral contraceptives, been pregnant or breast-feeding, or undergone abortion or other medical treatment which interfered with normal endocrine function

Therefore, the actual number of subjects included in the analysis were 475 athletes and 606 non-athletes. For the purpose of this study, the athletes were broadly categorized as follows: ball game players (basketball, field hockey, handball and volleyball, $n = 134$); racket game players (badminton, lawn tennis, table tennis, and squash rackets, $n = 94$); distance runners (800 m, 1500 m, and 5000 m, $n = 51$); and sprinters (100 m, 200 m, and 400 m, $n = 57$). Other categories were, jumpers (high jump and long jump, $n = 48$); throwers (shot put, discus and javelin, $n = 53$); and swimmers (100 m, 200 m, and 400 m, $n = 38$). The average weekly training periods of the athletes ranged from 8 to 16 h. The non-athletes who were of comparable age never actively participated in competitive sports. Before the collection of data, the purpose and procedure of this study were explained to the subjects who gave written informed consent.

Anthropometric measurements

Subjects' height and weight were measured using standard techniques and equipment. Body fat was estimated from the skinfold measures at three sites: triceps, subscapular and suprailiac. The skinfold measurements were made with Harpenden calipers according to the procedure suggested by Katch & Katch (1980). Subjects' percentage of body fat was predicted from their skinfold measurements using the nomogram of Sloan & Weir (1970). Relative weight for height was calculated using the Livi index:
$10\sqrt[3]{\text{weight(kg)}}/\text{height(m)}$ (Olivier 1969).

Questionnaires

Questionnaires were answered by the subjects between November 1984 and February 1985. The questionnaire included items about menstrual and reproductive history, use of oral contraceptive, chronological age, and athletic activity. Age at menarche was ascertained using recall procedures (Livson & McNeill 1962, Damon *et al.* 1969). The retrospective technique has been demonstrated to be a valid and reliable method of determining the menarchal age (Damon & Bajema 1974). Subjects were requested to indicate their ages when they first started to menstruate and whether they commenced regular sports activity before or after menarche. After a decision was made, each subject was further requested to assess her recall of menarche as either: not yet, uncertain or unwilling to respond; approximate or fairly certain; or certain. For all subjects, age at menarche was determined from their birth dates which have been accurately documented. The subjects were at least 3 years post-menarche at the time of this study.

Menstrual characteristics were defined as: regular normal menses, menstrual cycles between 23 and 35 days in length during the previous year and without menstrual disturbance; irregular menses, menstrual cycles shorter than 23 days or longer than 35 days at least three times in the previous year without any other menstrual disturbance. Other menstrual characteristics included oligomenorrhoea or secondary amenorrhoea (O/A), a missed menstrual period at least three times during the previous year; dysmenorrhoea, painful menstruation characterized by cramp-like pains in the lower abdomen, headache, irritability, mental depression,

Table 1. Physical characteristics of athletes and non-athletes

	Age (years)	Age at menarche (years)	Height (cm)	Body weight (kg)	Percent body fat	Livi index
Non-athletes (n=606)	24·5(1·2) (range 19–28)	13·10(0·9)*	166·2(5·7)	60·2(4·2)*	23·5(2·6)*	23·9(0·7)
Athletes (n=475)	24·1(1·7) (range 18–26)	14·32(1·8)	167·4(4·9)	56·7(3·8)	17·8(2·4)	24·1(0·6)
Ball game players (n=134)	24·2(1·8)	14·21(1·6)	169·5(4·2)	56·3(4·1)	19·6(2·5)	24·5(1.6)
Racket game players (n=94)	23·6(1·2)	13·84(1·5)	167·3(4·8)	57·5(3·8)	18·5(1·8)	25·1(1·4)
Jumpers (n=48)	23·5(2·1)	13·67(1·8)	166·7(5·3)	57·8(3·4)	19·2(3·1)	24·2(2·3)
Throwers (n=53)	24·6(2·3)	14·22(1·5)	166·6(4·1)	56·5(4·0)	19·4(2·6)	25·3(1·3)
Sprinters (n=57)	24·6(1·8)	14·62(2·1)	168·5(5·3)	56·7(4·2)	18·1(1·8)	24·2(1·5)
Distance runners (n=51)	25·0(3·1)	14·84(1·9)	169·2(4·3)	51·5(2·7)†	14·1(2·0)‡	21·2(1·1)†
Swimmers (n=38)	24·7(2·3)	13·82(1·2)	168·6(6·1)	56·1(4·2)	21·5(2·2)	23·9(1·6)

*Significantly different from athletes ($P<0·05$), t-test.
†Significantly different from other groups of athletes ($P<0·01$), Newman-Keuls test.
‡Significantly different from ball game and racket game players ($P<0·01$), Newman-Keuls test
Results are means (SD)

malaise and fatigue at least five times in the previous year; and menorrhagia, profuse menstrual flow due to no demonstrable anatomical or pathological lesion at least five times in the previous year.

Statistical anaylsis

Statistical analysis used Student's t-test and one-way analysis of variance (one-way ANOVA). When an F statistic indicated significant difference, Newman-Keuls post-hoc method (Hinkle *et al.* 1979) was applied on the ordered means to determine which of the means were significantly different from each other. A probability level of $\leq 0·05$ was taken to indicate significance.

Results

Some descriptive characteristics of the subjects are presented in Table 1. The non-athletes were significantly heavier and fatter ($P<0·05$) than the athletes. Results showed that the distance runners weighed considerably less, had strikingly lower percent body fat and Livi index values than the other groups of athletes ($P<0·01$).

The physical characteristics of the subjects according to their menstrual categories are given in Table 2. In general, body size, fat and weight appeared to be importantly related to menstrual dysfunction in the athletes. The oligo/amenorrhoeic athletes were significantly lighter ($P<0·05$) than the athletes with regular, normal menses and menorrhagia. In the athletic group, body weight, fat and Livi index values were highest in athletes with regular, normal menses. The overall mean age at menarche in the athletes was significantly retarded ($P<0·05$) compared with control subjects (Table 1). Similarly, age at menarche was delayed in athletes who started regular sports competition before the onset of menstruation (mean 14·10, SD 1·1 years) as distinct from those who commenced regular sports activity after menarche (mean 13·72, SD 1·0 years), but this difference was not statistically significant.

Table 3 shows the classification of subjects according to menstrual categories. Among the athletes, irregular menses (26%) and O/A (21%) were much more common than in the

Table 2. Physical characteristics of athletes and non-athletes according to menstrual categories (mean ± SD)

	Menstrual categories					
Variable	Regular, normal menses	Irregular menses	O/A	Dysmenorrhoea	Menorrhagia	P^*
Athletes ($n=475$)						
No. of subjects	102	125	101	80	67	
Age (years)	23·1(2·6) (range 18–25)	24·1(1·9) (range 19–26)	23·8(1·7) (range 19–25)	23·6(2·0) (range 18–25)	24·3(2·1) (range 18–26)	NS
Menarchal age (years)	14·21(1·5)	14·52(1·2)	14·60(1·1)	14·31(1·0)	14·42(1·6)	NS
Height (cm)	167·2(6·1)	167·4(6·3)	167·5(7·1)	166·8(6·3)	167·5(7·2)	NS
Body weight (kg)	58·3(5·1)	56·5(4·2)	54·6†(4·1)	57·7(3·8)	58·2(6·0)	$P<0{\cdot}01$
Percent body fat	20·5(3·2)	19·6(3·1)	15·4‡(2·2)	18·7(2·5)	18·6(2·4)	$P<0{\cdot}01$
Livi index	26·4(1·2)	23·1(1·1)	20·2§(0·8)	24·6(1·4)	26·1(1·5)	$P<0{\cdot}05$
Non-athletes ($n=606$)						
No. of subjects	303	108	49	95	52	
Age (years)	24·1(3·1) (range 19–26)	23·8(2·7) (range 20–25)	24·2(3·1) (range 19–27)	24·5(2·6) (range 19–27)	24·3(2·6) (range 20–28)	NS
Menarchal age (years)	13·01(1·2)	13·42(1·6)	13·61(1·4)	13·12(1·2)	13·30(1·5)	NS
Height (cm)	165·5(5·1)	166·2(5·7)	166·3(5·2)	165·8(6·1)	166·7(6·6)	NS
Body weight (kg)	60·3(4·6)	59·9(5·2)	60·4(5·6)	60·1(6·0)	61·5(6·2)	NS
Percent body fat	24·8(3·1)	24·4(3·4)	22·8(2·6)	23·2(2 8)	23·9(3·1)	NS
Livi index	24·6(1·5)	24·1(2·0)	24·2(1·8)	23·8(0 9)	24·1(1·1)	NS

Results are means (SD).
*One-way ANOVA
†Significantly different from athletes with regular, normal menstruation, $P<0{\cdot}01$, Newman-Keuls test.
‡Significantly different from athletes with regular and irregular, menstruation, $P<0{\cdot}01$, Newman-Keuls test.
§Significantly different from athletes with regular, normal menstruation and menorrhagia, $P<0{\cdot}05$, Newman-Keuls test
NS, Not significant; O/A, oligomenorrhoea or secondary amenorrhoea.

control subjects (18% and 8%, respectively). Furthermore, menstruation was more regular and normal in the non-athletes (50%) than the athletes (22%). A subdivision of athletes into sports activity groups showed that menstruation was most regular and normal in throwers (42%) and least regular in distance runners (8%). The incidence of O/A was more common in distance runners (51%) and ball game players (35%) than in the other groups of athletes. The swimmers (37%) and jumpers (25%) had more dysmenorrhoea than the athletes in other sports. Except for the high incidence of menorrhagia found in the sprinters (42%), the prevalence of menorrhagia among the athletic groups was generally low.

The subjects were grouped in terms of age at menarche and further categorized according to sports activity, and menstrual function. It was found that O/A was relatively more prevalent in the athletes ($n=85$) who started regular sports activity before menarche (43%). In contrast, menstruation was more regular and normal in athletes ($n=390$) who commenced active sports participation after menarche (40%). A 34% prevalence of O/A was found in the pre-menarche trained distance runners ($n=15$) as compared with 15% for their post-menarche

Table 3. Menstrual categories of athletes and non-athletes

	Regular, normal menses	Irregular menses	O/A	Dysmenorrhoea	Menorrhagia
Ball game players ($n=134$)	20(15%)	40(30%)	47(35%)	11(8%)	16(12%)
Racket game players ($n=94$)	25(27%)	26(27%)	13(14%)	20(21%)	10(11%)
Jumpers ($n=48$)	14(29%)	16(33%)	4(8%)	12(25%)	2(4%)
Throwers ($n=53$)	22(42%)	9(17%)	3(6%)	10(19%)	9(17%)
Sprinters ($n=57$)	7(12%)	14(25%)	3(5%)	9(16%)	24(42%)
Distance runners ($n=51$)	4(8%)	14(27%)	26(51%)	4(8%)	3(6%)
Swimmers ($n=38$)	10(26%)	6(16%)	5(13%)	14(37%)	3(8%)
Total athletes ($n=475$)	102(22%)	125(26%)	101(21%)	80(17%)	67(14%)
Non-athletes ($n=606$)	303(50%)	108(18%)	49(8%)	95(16%)	51(8%)

O/A, Oligomenorrhoea or secondary amenorrhoea.

trained counterparts. No other distinctive pattern of menstrual function was noted among the athletic groups.

Discussion

The subjects of this study varied considerably in their menstrual characteristics. It was noted that regular participation in competitive sports is associated with menstrual disturbances among the athletes. In general, an irregular menstrual cycle and O/A were the most common disorders in the athletes. In agreement with those of previous studies (Carlberg & Riedesel 1979; Frisch *et al.* 1980; Sanborn *et al.* 1982) the present results indicate that menstrual abnormalities were comparatively more common in athletes whose events were stressful. The ball game players and distance runners had the most common occurrence of O/A, while dysmenorrhoea and menorrhagia were most prevalent in the swimmers and sprinters, respectively.

According to Shangold (1982) athletes of low weight may be more subjected to hypoestrogenic amenorrhoea resulting from inadequate gonadotrophin stimulation to the ovaries and inadequate oestrogen production in scanty fat tissue. In this study, body weight, percent body fat and Livi index values were markedly lower in athletes having irregular menses and O/A, and higher in athletes with regular, normal menses and menorrhagia. Similarly, very low body fat, weight and Livi index scores were obtained for the distance runners who were largely oligo/amenorrhoeic. Since regular sports activity of high intensity could result in significant body fat and weight changes, the possibility that strenuous exercise can induce menstrual cycle irregularities cannot be totally excluded.

A significantly delayed menarche, and overwhelmingly greater incidence of menstrual disturbances in pre-menarche trained athletes in contrast to post-menarche trained athletes have been reported in the literature (Frisch *et al.* 1981; Lutter & Cushman 1982; Wakat *et al.* 1982). This is substantiated by the results of the present study which indicate delayed onset of menstruation and strikingly higher occurrence of menstrual disorders in athletes who commenced regular sports activity before menarche. Delayed menarche in Nigerian athletes who started regular sports activity before menstruation has been reported previously (Mathur & Toriola 1982).

On the question of whether menstrual problems could affect sports performance, the majority of athletes having menstrual disturbances (54%) admitted that these abnormalities have had no substantial effects on their performances, while only a few (27%) gave contrary response. Generally, the athletes did not envisage the possibility that these menstrual problems would detract from their interest to participate in sports competition in future.

Although results of several studies suggest a higher prevalence of menstrual disorders in athletes as contrasted with their non-athletic peers, the influence of these menstrual disturbances on athletes' reproductive function has not been clearly established. However, evidence from clinical studies generally support that sports participation does not adversely affect childbearing or childbirth but, on the contrary, has favourable effects on the female reproductive system (Erdelyi 1962; Zaharieva 1965).

An important limitation of this study was the questionnaire method used for the collection of data. Therefore, it was difficult to obtain more detailed information about the subjects' menstrual characteristics. A direct interrogation of the subjects would probably be more informative, but this was not feasible in the present study since the subjects were drawn from several states of Nigeria. This limitation should be considered in interpreting the results.

Since numerous psychological and physiological factors interact with physical exercise to account for the occurrence of menstrual dysfunction in athletes, similar studies in future should embark upon a longitudinal assessment of the female athlete to further elucidate the influence of regular sports activity on female reproductive function.

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Steroid receptors in human ovarian malignancy. A review of four years tissue collection

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Summary. The oestrogen and progestogen receptor status in ovarian cancers from 72 patients was correlated with histological type, primary or secondary origin and peripheral hormone concentrations. Changes occurred in receptor status during malignant transformations of ovarian tissues, with those for oestrogen being found more often, and those for progestogen less often than in non-diseased ovarian fragments. It is suggested that the similarity in sex steroid receptor content between ovarian and breast cancers warrants prospective study of ovarian sex steroid receptor status as a predictive index of survival and response to hormonal therapy in multi-centre clinical trials. Additional data on androgen receptors are also presented.

In recent years several studies have investigated receptors for steroid hormones in ovarian tumours, but the results generally have been variable (Table 1). Furthermore, differences in assay methodology, the small numbers of samples often studied and the range of different tumour types examined have made it difficult to draw conclusions from amalgamated data. This laboratory has previously published pilot results from 49 malignant ovarian tumours and suggested that determination of oestrogen and progestogen receptors (ER and PR respectively), in such tissues, might provide a useful index for response to hormonal or cytotoxic therapy (Willcocks *et al.* 1983), thus reflecting the experience gained in studies of human breast cancer (Vihko & Isotalo 1981).

This paper now reports the culmination of 4 years work on the receptor status of ovarian cancers in 72 patients who attended the Gynaecological Oncology Clinic at Westmead Hospital. The complete data cover the receptor status of both primary and metastatic disease and now include studies on androgen receptor status and possible correlation with peripheral blood hormone levels

Subjects and methods

Specimens were obtained from 108 women undergoing surgery for ovarian tumours and were subsequently classified as benign in 36 and malignant in 72. No subject had had endocrine treatment before surgery. The 100 malignant tissues (both primary and secondary tumours) were further classified according to criteria recommended by the WHO (Serov *et al.* 1973) as serous papillary 54; mucinous 17; endometrioid 21; undifferentiated 4; and clear cell 2. One tumour (two specimens) was classified as 'small

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cell' (Dickersin *et al.* 1982). Of these, 41 were designated as well-differentiated and included seven of low potential malignancy. Nine of these 72 patients were premenopausal (<45 years), 36 perimenopausal (>45–<55 years) and 27 postmenopausal (>56 years). The 40 benign neoplastic tissues (samples were obtained from both ovaries in four patients) included 26 cystadenoma, seven cystic teratoma and seven fibroma.

Details of the method of tissue collection, cytosol preparation, and binding assays for oestrogen and progestogen receptors have been described previously (Willcocks *et al.* 1983). Androgen receptors (AR) were assayed in the same fashion: duplicate 100 µl aliquots of cytosol were incubated with five graded concentrations (10–0·33 nmol/l) of the synthetic corticosteroid 3H-R1881; displacement used authentic R1881. The synthetic glucocorticoid triamcinolone acetonide (TA) was used to block binding to progestogen, glucocorticoid and mineralocorticoid receptors. All tumours with values >1 fmol/mg of cytosol protein were considered positive, although the significance of values below 10 fmol/mg may be questionable.

For the preliminary study concerning the relation between peripheral circulating hormones and steroid receptors, peripheral venous blood was collected from the patient at the time of operation when tissue was taken for receptor analysis. All concentrations of hormones (LH, FSH, prolactin, oestradiol, progesterone, 17-hydroxyprogesterone, dehydroepiandrosterone sulphate and testosterone) were determined using commercially available radioimmunoassay kits. The sera were assayed amongst other routine samples at the Institute of Clinical Pathology and Medical Research, Westmead.

Table 1. Previous reports on oestrogen (ER) and progestogen (PR) receptors in ovarian tumours

Authors	Year	Classification	Number of samples	Percentage of receptor-positive tumours	
				ER	PR
Kiang & Kennedy	1977	Malignant	5	40	—*
Friberg *et al.*	1978	Malignant	4	25	—
		Benign	4	25	—
Holt *et al.*	1979	Malignant epithelial	16	50	19
Grilli *et al.*	1979	Malignant	10	60	60
Dapunt *et al.*	1979	Malignant	57	50	32
Friedman *et al.*	1979	Malignant	34	100	100
Bibro *et al.*	1979	Malignant epithelial	29	100	—
Stedman *et al.*	1980	Malignant	11	45	25 (4 samples)
Janne *et al.*	1980	Malignant	21	71	38
		Benign	29	83	86
Holt *et al*	1981	Malignant epithelial	29	83	—
Galli *et al*	1981	Malignant	18	67	50
		Benign	5	40	20
Creasman *et al.*	1981	Malignant	18	61	27
Bergqvist *et al.*	1981	Malignant	13	67	40
		Benign	20	35	45
Hamilton *et al.*	1981	'Ovarian tumours'	19	32	—
Hahnel *et al.*	1982	Malignant epithelial	22	45	20 (15 samples)
Quinn *et al*	1982	Malignant epithelial	33	52	34 (32 samples)
Schwartz *et al*	1982	Malignant epithelial	30	97	—
Ford *et al.*	1983	Malignant epithelial	39	38	15
Bojar & Petzinna	1983	Malignant epithelial	53	66	45
Jones *et al.*	1983	Malignant	42	81	45
Kauppila *et al.*	1983	Malignant	68	88	81
Lantta-Hytonen	1984	Malignant	50	50	44
Gronroos	1984	Malignant	21	62	57
This study		Malignant	100	53	40

* PR not assayed.

Table 2. Distribution of oestrogen (ER) and progestogen (PR) receptors in ovarian tissues

Receptor status	Normal ovary	Benign tumours	Malignant tumours
ER +ve, PR +ve	6 (16%)	2 (5%)	27 (27%)
ER +ve, PR −ve	1 (3%)	5 (13%)	25 (26%)
ER −ve, PR +ve	21 (57%)	7 (17%)	13 (13%)
ER −ve, PR −ve	9 (24%)	26 (65%)	34 (34%)
Total specimens	37	40	100
Total patients	33	36	72

Results

Preliminary results defining collection of tissues

It has been noted that the handling of tissues before their arrival at the laboratory for receptor assay can contribute to variation (Smith 1980; Koenders *et al.* 1978). In a small study the effect of time difference between collection and processing was investigated. Fragments of tissue were immediately placed in liquid nitrogen at the time of excision and transported to the laboratory for subsequent assay, or left for 1 h at room temperature before preparation. The results from 11 cases showed that as long as tissues were frozen within 1 h of collection no statistically significant change in receptor content could be demonstrated. Since it has been shown previously that approximately 30% of receptors are apparently 'lost' once tissue is frozen (Toppila *et al.* 1982), to allow comparison before assay, all samples in this study were stored for no longer than 8 weeks in liquid nitrogen.

Receptor status of patients

Of the 100 tissues of malignant ovary studied 66% contained ER and/or PR (Table 2). By comparison, in ovarian tissue taken from benign tumours oestrogen and progestogen receptors were only detected in 35% of specimens. Normal adult ovary, although not valid for comparison because of the compartmental structure of the organ (e.g. follicles, corpora lutea, stroma), showed some receptor binding in 76% of samples.

In malignant ovarian tissues ER were present in 53% of samples at (Table 3) concentrations ranging from 1 to 151 fmol/mg cytosol protein. Of these, 31% had concentrations greater than 10 fmol/mg protein, sometimes the upper limit of an equivocal result in reporting receptor values for breast tissue. Furthermore, the concentration of ER in malignant ovarian tissue was significantly greater ($P<0{\cdot}01$) than in non-diseased ovary or benign tumours (Table 4). Progestogen receptors were detectable in 40% of malignant tumours being deficient by comparison with unselected non-diseased ovarian fragments (73%).

The receptor status of tissues with different histological classes of malignancy are given in Table 3. As might be expected endometrioid tumours were generally positive for both receptors, while mucinous tumours were generally negative. There was a random distribution in serous material, and our examples of rarer forms, e.g. small and clear cell carcinoma, lacked receptors even though clear cell carcinoma is regarded by some as a variant of the endometrioid group (Curling & Hudson 1975). A summary of the concentrations of receptors in these tissues is given in Table 4. The mean value for ER content was highest in serous carcinoma and lowest in endometrioid carcinoma, but the pattern was reversed for PR. There was no significant difference between the subgroups of poorly differentiated and well differentiated tumours and those of low potential malignancy, although the well differentiated tumours had a marginally greater receptor content. In 11 subjects with malignant ovarian disease the presence of androgen receptors could not be demonstrated.

Table 3. Distribution of oestrogen (ER) and progestogen (PR) receptors in different malignancies of the ovary

Receptor status	Serous	Mucinous	Endometrioid	Small cell	Undifferentiated	Clear cell	Total (%)
ER +ve, PR +ve	15	2	10	—	—	—	27 (27)
ER +ve, PR −ve	20	2	3	—	1	—	26 (26)
ER −ve, PR +ve	3	3	5	1	1	—	13 (13)
ER −ve, PR −ve	16	10	3	1	2	2	34 (34)
Number of specimens	54	17	21	2	4	2	100

Table 4. Receptor concentrations (fmol/mg protein) in different tissues of ovarian origin

Type	No. of specimens	Receptor concentration (fmol/mg protein)					
		ER positive			PR positive		
		n	Mean	Range	*n*	Mean	Range
Serous	54	35	30	1–151	18	27	7–120
Mucinous	17	4	26	4–56	5	95	16–272
Endometrioid	21	13	13	1–37	15	114	1–604
All malignant	100	52	26	1–151	38	71	1–604
Benign	40	7	9	2–32	9	81	29–337
Non-diseased	37	7	6	2–9	27	127	5–339

Relation between primary and secondary tumours from the same patient

The combination of measurable ER and PR occurred less often in metastases than in primary tumours (Table 5), although when the presence or absence of any one receptor was considered there were no significant differences. ER occurred more often in metastases than in primary tumours (χ^2 test, $P<0{\cdot}05$), but for PR the pattern was reversed with receptors present less often in metastases ($P<0{\cdot}001$). When the data were examined from 15 patients in whom both primary and secondary deposits were removed (Table 6), the above pattern generally held. Four subjects had no ER in their primary lesion and although three values for the secondary were <5 fmol/mg protein, one subject had a concentration of 58 fmol/mg protein in her metastatic deposit. Similarly, two patients had no PR in the primary while values of 50 fmol/mg protein and 89 fmol/mg protein occurred in the secondaries, the former patient having a similar pattern for ER.

Relation between plasma hormones and receptor status

The median and interquartile values for each of the hormones in the study groups are given in Table 7. Essentially, there were no differences between these values and those obtained for an age-matched group of women in whom no clinical diagnosis of cancer was apparent. Not unreasonably (since some of the corresponding tissue samples had no detectable concentrations of receptor present) there was no correlation between any of the hormone values and the corresponding steroid receptor status.

Discussion

Drawing conclusions from amalgamation of the results from previously published studies of steroid receptor assays is not always useful because of different assay methods, the different tumour types, and in some cases the limited number of patients examined in each study. However, the data from the present larger study confirm the results shown in the few large series (Dapunt *et al.* 1979; Bojar & Petzinna 1983; Kauppila *et al.* 1983; Lantta-Hytonen 1984). One recent study (Kauppila *et al.* 1983) examining 68 tissues reported the frequency of cytosol ER and/or PR in epithelial ovarian tumours as high as 88% and 81% respectively.

In our study the receptor pattern of all 177 ovarian samples (100 malignant, 40 benign, 37 non-diseased ovary) showed that ER were more often found in malignant neoplasms (53%) than in benign (17%) and in non-diseased ovaries (19%), a pattern consistent with that of Vierikko *et al.* (1983). In contrast however, PR were less frequent in malignant epithelial tumours (40%) and in benign tissues (22%) than in non-diseased ovaries (73%). The presence of PR alone occurred in only a small proportion of tumour

Table 5. Receptor status of primary and metastatic lesions of epithelial ovarian malignancies

Receptor status	Primary (n = 60) *n* (%)	Metastatic (n = 40) *n* (%)
ER +ve	27 (45)	26 (65)
PR +ve	32 (53)	8 (20)
ER +ve, PR +ve	20 (33)	7 (17)
ER +ve, PR −ve	7 (11)	19 (47)
ER −ve, PR +ve	12 (20)	1 (2)
ER −ve, PR −ve	21 (35)	13 (32)

tissues but was relatively common in non-diseased tissue. The large proportion of 'normal' ovarian tissues containing measurable PR only may indicate that PR synthesis is not regulated by oestrogen action alone, or it could be an artefact of the cell type (e.g. granulosa) taken for assay, or may indicate that PR is expressed at lower cytosol ER concentrations in non-diseased tissues than in malignancy (Vierikko *et al.* 1983). In this respect the receptor status of non-diseased ovary resembles that of endometriotic tissues (Toppila *et al.* 1983). Nevertheless it can be concluded that changes occur in the regulation of steroid receptors during malignant transformation of ovarian tissues, and the results of this extended study confirm the earlier report on fewer patients (Willcocks *et al.* 1983).

The absence of measurable AR in the 11 ovarian neoplasms studied confirms the findings of Quinn *et al.* (personal communication) where 41 of 64 ovarian tissues examined were similarly devoid of measurable AR. However, these findings contrast with those of Friberg *et al.* (1978), 4 of 8 negative; Galli *et al.* (1981), 5 of 23 negative; Kusanishi *et al.* (1982), 0 of 2 negative; and Hamilton *et al.* (1981), 2 of 16 negative. Differences in assay methodology (i.e. radioligands and competitors) are perhaps responsible for the even larger discrepancies than already exist for ER and PR between series, but the release of a new synthetic androgen for receptor studies (Mibolerone: Amersham (Australia) Pty Ltd, Surry Hills, N.S.W.), may help resolve these differences in the future.

Whereas Ford *et al.* (1983) could find no receptor binding in the mucinous tissues they studied, some mucinous tumours in this series had low but detectable ER (4 of 17). For all tissues that were receptor-positive there appeared to be an inverse relationship between the mean values for ER and PR concentration in the classification order: serous; mucinous; endometrioid (Table 4). Since PR are regulated by oestrogen action this may simply indicate incomplete oestrogen action in serous tissues. Rome *et al.* (1981) have suggested that mucinous and endometrioid tissues excrete more oestrogen than do serous malignancies, but Quinn *et al.* (1982) noted that translocation of the steroid-receptor complex to the nucleus may have occurred, or that all cytoplasmic receptors were occupied and not detected by the assay. A typical feature of endometrioid tumours, demonstrated by Vierikko *et al.* (1983) and confirmed in this study, is the high incidence of both ER and PR positive tissues and the high PR/ER ratio.

When tumours from the same patient were classified as primary or metastatic, the metastases generally retained ER while fewer (4 of 9) had PR. Furthermore, we have shown for the first time that metastases may contain receptors even in the absence of binding in the primary lesion. By contrast, in other studies receptor binding occurred in metastases only if there was binding in the primary tumours (Holt *et al.* 1979;

Table 6. Comparison of receptor status between primary (P) and metastatic (M) ovarian tumour tissues in the same individual

		Relation between receptor levels in P and M tissues		
		P>M	P<M	P = M
Receptor	No. of patients	*n* (%)	*n* (%)	*n* (%)
Oestrogen	15	1 (7)	6 (40)	8 (53)
Progestogen	15	6 (40)	5 (53)	4 (27)

Table 7. Concentrations of peripheral circulating hormones in patients with malignant or benign ovarian tumours

Hormone	Ovarian carcinoma (*n* = 18)	Benign ovary (*n* = 13)	Normal postmenopausal reference value
LH (i.u./l)	18·4 (8·0–36·0)	10·0 (7·6–25·0)	>38
FSH (i.u./l)	19·5 (9·8–27·0)	4·4 (2·9–21·5)	>8
Prolactin (mU/l)	1392·0 (388–5034)	1893·0 (209–2401)	<350
Oestradiol (pmol/l)	63·0 (44·0–229)	107·0 (28·0–335)	<100
Progesterone (nmol/l)	2·9 (1·2–6·5)	7·1 (1·9–12·3)	<5
17-hydroxyprogesterone (nmol/l)	2·5 (1·2–8·1)	5·2 (2·6–5·8)	<6
DHEAS (μmol/l)	2·9 (1·2–4·4)	6·0 (1·6–7·9)	<2
Testosterone (nmol/l)	1·3 (0·5–2·6)	1·9 (1·6–2·5)	<3

Values are medians with interquartile ranges shown in parenthesis.

Bergqvist *et al.* 1981), or similar receptor combinations were found in both primary and metastatic tumours (Bojar & Petzinna 1983). In carcinoma of the breast, oestrogen binding was found to be less frequent in metastatic than in primary tumours ($n = 604$, Vihko & Isotalo 1981), although the difference was only small (8%) and may not be clinically relevant. Confirmation of the above findings for the ovary must await further collection of tissues.

Few studies have surveyed the hormonal profiles in the peripheral circulation of patients with ovarian cancer. When this has been determined, the results have not been correlated with receptor status (Jeppsson *et al.* 1982; Heinonen *et al.* 1982; Waxman 1984). The data from this pilot study of 53 subjects, in whom the peripheral circulating hormone concentrations and the corresponding steroid receptor content were available, are limited by several factors. Firstly, although most patients (64%) were postmenopausal, no allowance was made for the phase of the ovarian cycle in the others. Secondly, blood samples were obtained during the operation when tissue appropriate for receptor studies was identified, thus allowing for direct 'real time' comparison, but we could not investigate the effects of anaesthesia or operation on hormone concentrations although it is known that some can increase under stress such as occurs during surgery. We have not accounted for some discrepancy in the gonadotrophin results in the ovarian cancer patients most of whom were postmenopausal. Moreover, we were unable to determine levels of oestrone, the major postmenopausal oestrogen.

Finally, since many tissues contained no detectable receptors for steroids, there were insufficient numbers for correlation within subgroups. Thus even though our own (Willcocks *et al.* 1983, Toppila *et al.* 1983) and other studies have indicated the presence of steroid receptors in malignant tissues arising in Mullerian-derived structures of the female genital tract (namely surface ovarian epithelium, oviduct, endometrium and endocervix) the results suggest that further detailed analysis of the peripheral hormone status, as an aid to interpreting steroid receptor status, is unlikely to be rewarding Therefore, as in breast cancer (Vihko & Isotalo 1981) it is suggested that there are neither clinical nor academic reasons for ordering these investigations as a guide to prognosis in patients with ovarian cancer.

Finally, because malignant tumours are heterogeneous, all cell populations can contain hormone-dependent receptor-positive cells, and hormone-independant receptor-negative cells in varying proportions. Therefore, steroid receptor measurements will give additional information that is not available by conventional histological and staging characterization of ovarian carcinoma. It is also suggested that, for the present at least, only the presence or absence of receptors should be used in clinical practice until standards for determining ER and PR 'positivity' are defined in large multi-centre trials. The recent commercial availability of 'kit' methods to determine ER (Abbott Diagnostics Division, North Ryde, N.S.W.) or an antibody to ER-associated protein (D5-antigen; Amersham (Australia) Pty, Ltd, Surry Hills, N.S.W.) may make this report one of the last surveys of receptors in malignant ovarian tissues using the classic methods.

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Langerhans' cell density in the normal exocervical epithelium and in the cervical intraepithelial neoplasia

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Summary. A morphometric analysis was performed of the Langerhans' cell density in epithelial sheets obtained from normal exocervices and from exocervices with squamous carcinoma. Laminae of exocervices with squamous carcinoma that showed cervical intraepithelial neoplasia (CIN) were classified according to its predominant degree of severity as CIN I, CIN II and CIN III or as normal when no neoplastic changes were found. Laminae with CIN showed a higher Langerhans' cell density than the laminae from normal exocervices and than the normal laminae of exocervices with carcinoma. The magnitude of the increase of Langerhans' cell density and the degree of severity of the neoplastic changes appear as closely related phenomena. An increase of the more ramified types of Langerhans' cell in the laminae containing CIN was found, with the most ramified being more frequent in the most severe lesions.

The immunological function of the epidermal Langerhans' cell and its involvement in various cutaneous pathological processes has been widely investigated in the last 20 years. (Shelley & Juhlin 1978; Friedmann 1981), but there has been relatively little interest in Langerhans' cells in human exocervical epithelium and their possible role in cervical pathology. Indeed, after the electron microscopic detection of the Langerhans' cell in the human exocervical epithelium by Younes *et al.* (1968) and Hackemann *et al.* (1968) only a few publications dealing with the exocervical Langerhans' cell have appeared in the past few years. Figueroa & Caorsi (1980) described the morphology, density, distribution and ultrastructure of Langerhans' cells in the normal exocervical epithelium. Morris *et al.* (1983*a*) reported on the distribution and frequency of Langerhans' cells in the human exocervix with special emphasis on the transformation zone and the interrelations with T lymphocytes. Morris *et al.* (1983*b*) also studied Langerhans' cells in wart viral infection (WVI) and in cervical intraepithelial neoplasia (CIN) of the uterine cervix. Caorsi & Figueroa (1984) showed the presence of Langerhans' cells in the invasive buds of invasive squamous carcinoma of the cervix, in the lymphoid infiltrate of the chorion and in the coexistent CIN. Both Morris *et al.* (1983*b*) and Caorsi & Figueroa (1984) found an increased frequency of Langerhans' cells in CIN.

The present report deals with comparative analysis of the density of Langerhans' cells in epithelial sheets of both normal exocervical epithelium and neoplastic and non-neoplastic epithelial sheets obtained from women with cervical squamous carcinoma.

Subjects and methods

Uterine cervices with early invasive squamous carcinoma were obtained at total hysterectomy from four women aged 38, 45, 49 and 57 years.

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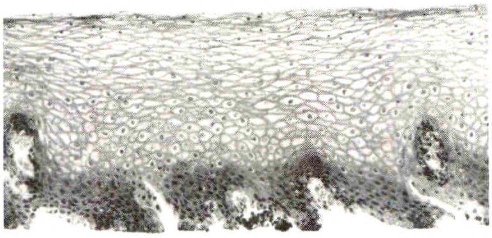

Fig. 1. Epithelial sheet from a normal exocervix showing the characteristic layered differentiation × 95.

From each of these cervices, 15–20 epithelial laminae were obtained. They were stained with a variant of the zinc-iodide-osmium (ZIO) method (Rodríguez & Caorsi 1978; Figueroa & Caorsi 1980). Two normal uterine exocervices were similarly processed.

Preparation of the epithelial laminae and staining with ZIO

Tissue fragments of approximately 6–15 mm^2 were used to obtain the epithelial sheets. The fragments were incubated at 37°C in buffered 20 mM EDTA (Scaletta & MacCallum 1972) for 1·5–2 h. After this treatment the epithelium could be readily separated from the chorion with fine forceps. The epithelial sheets thus obtained were stained with ZIO mixture at pH 7·4 for 18 h at 4°C with continuous agitation. The stained sheets were mounted on microscopic slides, coverslipped and studied under a conventional light microscope. Since these preparations included the whole epithelium, the entire profile of the Langerhans' cells, even its finest branches, could be visualized by operating the micrometer. The Langerhans' cell population/mm^2 and the density of each type of Langerhans' cell as previously described (Figueroa & Caorsi 1980; Caorsi & Figueroa 1984) could thus be reliably determined. Langerhans' cell density was expressed as a number of cells/mm^2.

Histological procedures

Once the Langerhans' cell population had been established, each epithelial sheet, adequately identified, was dismounted from the glass slide and embedded in paraplast. Serial cross sections of 5 μm thick were obtained from each sheet and stained with haematoxylin. The sections corresponding to each sheet were used to establish the presence or absence of neoplastic lesions and characterize the degree of malignancy following the criteria proposed previously (Buckley *et al.* 1982). This procedure allowed us to establish in each epithelial sheet the density of Langerhans'cells and the histological characteristics of the epithelium.

Statistical analysis

The statistical analysis was performed on a Digital 2020 Computer using the SPSS program (University of Pittsburg). A multiple comparison procedure (Scheffe's test) was performed in conjunction with analysis of variance and normality for variables (Kolmogorov-Smirnov's test). All the values are expressed as means (SEM).

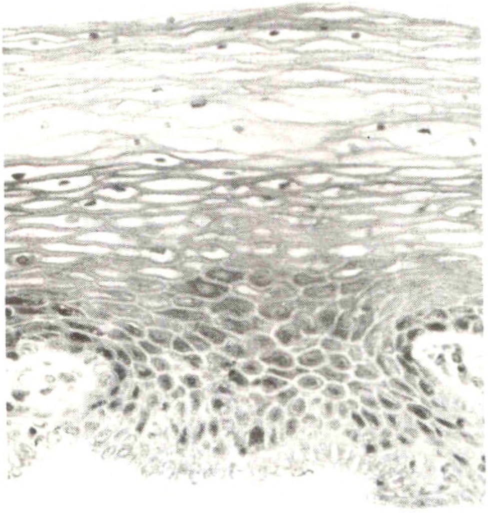

Fig. 2. Non-neoplastic epithelial sheet from an exocervix with squamous carcinoma. The stratification of the epithelium displays some abnormalities probably corresponding to a metaplastic process × 285.

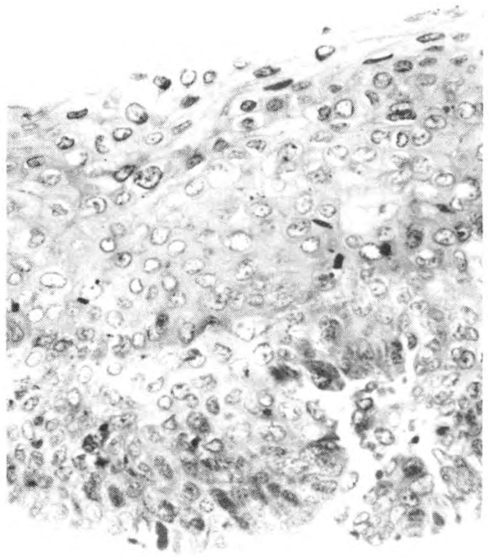

Fig. 3. Epithelial sheet (CIN I) from an exocervix with squamous carcinoma ×285.

Results

The histological sections of the dismounted epithelial sheets, which had previously been stained in block with ZIO and utilized for the determination of Langerhans' cell density, revealed excellent tissue preservation.

The epithelial sheets obtained from normal exocervices showed the typical layer differentiation (Fig. 1). Regarding the relative frequency of normal and neoplastic epithelial cells, the laminae from cases of squamous carcinoma were heterogeneous, so that non-neoplastic epithelium and CIN of various degrees could be found in the same lamina; the epithelial sheets obtained from these cases of squamous carcinoma did not show the lesions of wart virus infection.

Those laminae obtained from exocervices with squamous carcinoma were classified as (a) normal without neoplasia, although they could show other types of non-neoplastic alterations, such as parakeratosis or dyskeratosis (Fig. 2); (b) CIN I, mild neoplastic alterations (Fig. 3); (c) CIN II, neoplastic alterations predominantly of the moderate type (Fig. 4); (d) CIN III, neoplastic alterations predominantly of the severe type (Fig. 5). In the last three categories the epithelial sheets were classified according to the degree of CIN that extended over 50% of the epithelium, despite the fact that the remaining area could correspond to normal epithelium or lower degrees of CIN. Exceptionally, there were laminae in which a large area with mild or moderate lesions coexisted with small severe lesions; these laminae were excluded from the quantitative analysis, so that when a lamina was characterized as given degree of CIN, the remaining area of such a lamina was occupied by either normal tissue or lower degrees of CIN.

Langerhans' cell density in the different classes of laminae

Laminae with CIN showed a higher Langerhans' cell density than laminae belonging either to normal exocervices or to normal sheets of the exocervices with carcinoma. Furthermore, a correlation between Langerhans' cell density and degree of CIN could also be established, with CIN III displaying the highest density. (Fig. 6.)

The mean density of Langerhans' cells in epithelial sheets from normal exocervices was 10·4 (SEM 1·6) cells/mm^2. In cervices with squamous carcinoma the Langerhans' cell densities were in the various categories: Normal 13·3 (SEM 2·2) cells/mm^2; CIN I 37·1 (SEM 4·3) cells/mm^2; CIN II 48·3 (SEM 7·2) cells/mm^2; and CIN III 72·9 (SEM 4·2) cells/mm^2 (Fig. 6).

The test of multiple comparison applied to

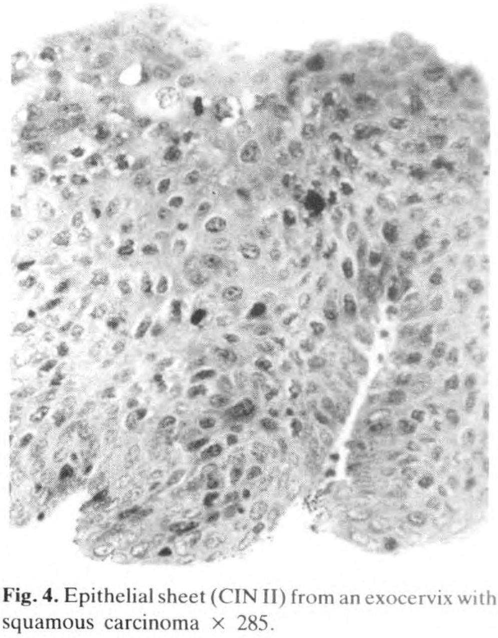

Fig. 4. Epithelial sheet (CIN II) from an exocervix with squamous carcinoma × 285.

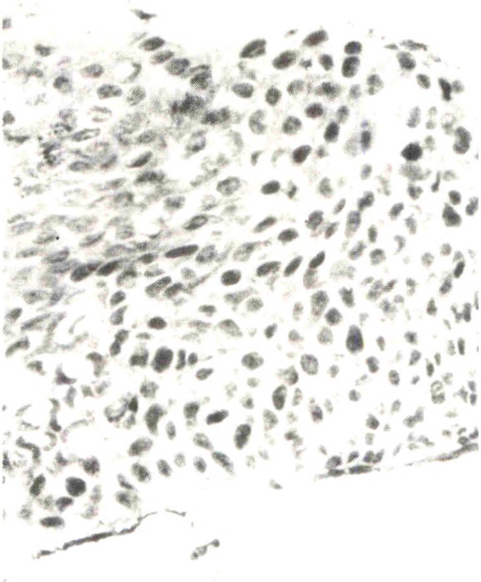

Fig. 5. CIN III in an epithelial sheet of a case with squamous carcinoma × 285.

these categories confirmed that the density of Langerhans' cells in CIN II and CIN III was significantly higher than in (i) CIN I and (ii) normal epithelial laminae ($P<0{\cdot}05$). Furthermore, this test also confirmed that the Langerhans' cell density in CIN III was significantly higher than in all other categories.

Density of the various types of Langerhans' cells in the different classes of laminae

The average density of the various types of Langerhans' cell for each one of the classes of epithelial sheets is shown in Fig. 7. The highest density of the most branched Langerhans' cells was found in the laminae with CIN. To compare the degree of branching of Langerhans' cells in the different classes of laminae, only two degrees of Langerhans' cell branching were considered, the least branched ones (Types 1, 2 and 3) and the most branched ones (Types 4, 5 and 6).

Laminae belonging to the normal exocervices revealed a predominance (79%) of the least branched Langerhans' cells. Similarly in the normal laminae of cervices with squamous carcinoma the least branched Langerhans' cells predominated (63·4%). In the CIN I laminae, both the least and the most branched Langerhans' cells had a similar frequency (51% and 49% respectively). On the other hand the most branched Langerhans' cells predominated in CIN II and CIN III (61·1% and 58·9% respectively).

The test of multiple comparison applied to the five classes of laminae shown in Fig. 7 confirmed that the density of the most branched Langerhans' cells was significantly higher in CIN I, CIN II, and CIN III than in the normal epithelial laminae ($P<0{\cdot}05$); and that the density of the most branched Langerhans' cells was significantly higher in CIN II and CIN III than in CIN I, and in CIN III than in CIN II ($P<0{\cdot}05$).

Discussion

Our findings provide new evidence with respect to the increase of Langerhans' cell density in CIN, moreover, they show, quite convincingly, that the magnitude of such an increase is in direct relation to the severity of neoplastic transformation.

Allowing for the fact that different degrees of CIN may coexist within a restricted area of epithelium, and since the laminae were relatively large, laminae displaying a homogeneous neo-

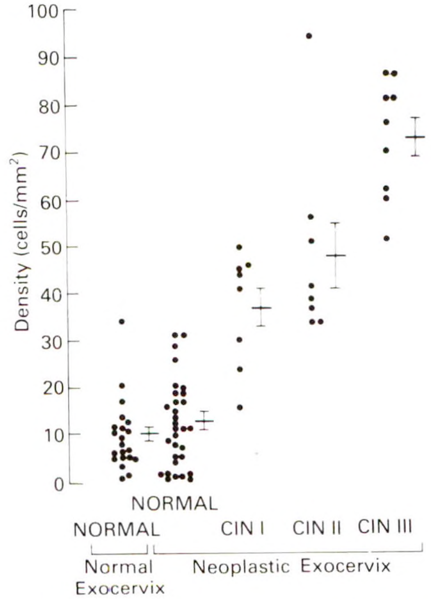

Fig. 6. Density of Langerhans' cells in epithelial sheets from normal and neoplastic exocervices. Each dot corresponds to the Langerhans' cell density in one epithelial sheet. Horizontal lines show mean and the vertical bars ± SEM values.

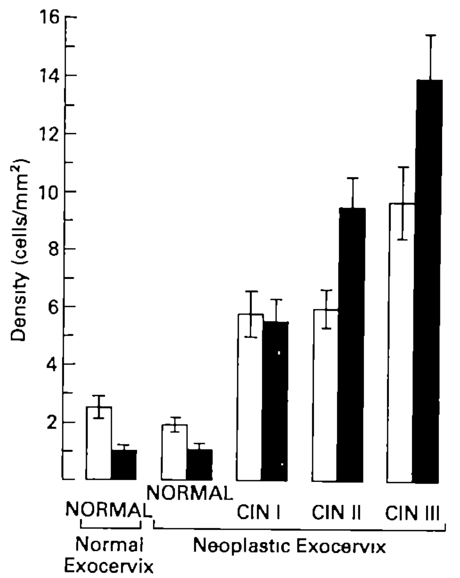

Fig. 7. Frequency of each type of Langerhans' cell in sheets from normal exocervices and in the neoplastic epithelial sheets. The dark bars represent the most branched types of Langerhans' cell (Types 4, 5 and 6).

plastic change were virtually impossible to obtain. And since the laminae were characterized only by the predominant lesion it is likely that the actual increase of Langerhans' cell density in the different types of CIN will be underestimated.

Caorsi & Figueroa (1984) pointed out that the increase in Langerhans' cell density in the squamous carcinoma of the exocervix could be due to a higher migration rate of Langerhans' cells from the bone marrow to the epithelium; to an intraepithelial proliferation of Langerhans' cells; or to a retention of Langerhans' cells in the neoplastic epithelium for periods longer than that of Langerhans' cells in a normal epithelium. Whatever the mechanism responsible for the increased density of Langerhans' cells in neoplasia, it is tempting to speculate about the probable reasons.

Morris *et al.* (1983*b*) found fewer or damaged Langerhans' cells in exocervical epithelium with wart virus infection (WVI). Similar findings have been described in skin irradiated with X-rays (Fan *et al.* 1959; Potten 1978; Cole *et al.* 1984; Groh *et al.* 1984) or with untraviolet light (Bergstresser *et al.* 1980; Aberer *et al.* 1981; Stingl *et al.* 1981; Iacobelli *et al.* 1983; Friedmann *et al.* 1983; Nithiuthai & Allen 1984). On the other hand, there is evidence which favours the view that WVI is somehow involved in the genesis of the cervical neoplasia (Ludwig *et al.* 1981; Reid *et al.* 1982; Crum & Levine 1984).

Furthermore, the carcinogenic effects of ultraviolet light and X-rays are well known (Cole & Nowell 1965; Albert 1976). Therefore, it seems reasonable to suggest that the damage and/or decrease of Langerhans' cell density caused by these agents could be a prerequisite for the development of their carcinogenic effect. Once the neoplastic lesion has developed, some kind of signal(s) from the neoplastic tissue could, in turn, trigger the increased frequency of Langerhans' cells in the neoplasia itself, through some of the mechanisms outlined above, namely migration, proliferation or longer retention.

Another similar suggestion has been advanced by Toews *et al.* (1980). They have suggested that Langerhans' cells 'may play a pivotal role in immune surveillance against skin malignancy' due to their capacity to capture and present antigens and induce a cellular immune response. Streilein *et al.* (1980) have also suggested that of the roles played by Langerhans' cells could be that of converting potentially tolerogenic signals into immunogenic ones, and that if this were the case, an epithelium devoid of Langerhans' cells may be vulnerable in several relevant ways.

In exocervical neoplasia not only does the Langerhans' cell density increase but also the degree of branching. We have previously suggested that the larger number of ramifications and branching may be related to a higher immunological activity (Caorsi & Figueroa 1984). An increase in the surface area of the Langerhans' cell could result in an enhanced capacity to bind antigens; and a greater chance to establish surface contacts with transient lymphocytes. All of this would make the immune response more efficient. In other words, the increased surface of the Langerhans' cell could make it a better sentinel (Toews *et al.* 1980; Streilein *et al.* 1980).

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A simple database system for an in-vitro fertilization programme using commercial software

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Summary. We present a simple database system for an IVF programme for use on a personal computer (IBM-PC) using commercial software (dBase II). The system permits storage of a basic set of data and automatic computation of 13 statistical variables.

One of the most promising uses of personal computers is in the field of data storage and retrieval. In contrast to the cost, size, and complexity of large mainframe computers, personal computers are particularly suited for applications in limited fields such as specialized outpatient clinics (Bingham *et al.* 1984; Lilford *et al.* 1983)

In-vitro fertilization (IVF) programmes require meticulous documentation from the time of a patient's acceptance into the programme up to the eventual birth of an infant. In addition, constant quality control of an IVF programme is essential, since its success depends on many different factors and declining fertilization or pregnancy rates have to be detected quickly in order to initiate the necessary improvements. Compared with conventional files a database offers the possibility of rapid retrieval of data and of computation of statistics. With these facts in mind we designed a simple database system for our IVF programme for use on a personal computer using commercial software.

Description of the program

Hardware and software

We used an IBM PC with 2 disk drives and 256 K RAM and 1 monochrome or colour monitor, and PC-DOS 2·0 operating system. The database system was written in dBase II version 2·4 (Ashton Tate, Culver City, California). dBase II uses database files for storage of data according to a predetermined structure, and program files containing a sequence of dBase II commands. Program files are responsible for the creation of menus and the screen displays for input and output, and for the computation of the statistics. The program files take about 15 K, and 100 records about 21 K. The program files and the structure of the database file for input of data can be adapted by any user familiar with dBase II.

System design

The system was not designed as a comprehensive data base for all relevant information in an IVF programme but rather for the storage and retrieval of a limited set of basic data from each treatment cycle. The requirements were that the system should be easy to use, that all relevant data permitting identification of particular patients should be easily accessible, and that statistics concerning the IVF programme should be available at any time (Johnson 1985). The system should not replace the traditional paper record. To protect confidentiality of patient data the database files should be on diskettes only.

The database system is entirely menu driven (Byers 1982). From the main menu four different options can be called:

1. enter oocyte retrieval
2. enter pregnancy
3. modify record
4. statistics

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Table 1. Screen format for entering oocyte retrieval

```
Oocyte retrieval                                                   Rec No:
==============================================================================
Date (YY/MM/DD):    /   /   :
Chart-No:                 :
Name:                                                  :        Age:    :
No. of previous oocyte retrievals:
------------------------------------------------------------------------------
Cycle stimulation (1-hMG, 2-Clom/hMG, 3-Clom, 4-FSH):                  :       :
No. of follicles on ultrasound:    :
------------------------------------------------------------------------------
Oestradiol (pg/ml)                        1:     :           2:      :
                                          3:     :           4:      :
                                          5:     :           6:      :
------------------------------------------------------------------------------
Cycle day at oocyte retrieval:    :
Oocyte retrieval (L-Laparoscopy, U-Ultrasound):    :
------------------------------------------------------------------------------
Sperm density (MIO/ml):    :
No. of oocytes retrieved:    :
No. of embryos transferred:    :

TEXT:                                          :
```

Table 1 shows the screen for oocyte retrieval with the information that can be entered. To enter a pregnancy the name of the patient has to be given; since many patients have several treatment cycles, the program displays the days of the different follicular punctures. The user then has to select the record corresponding to the date. The third option is similar to the first except for the fact that all information stored for a particular puncture is shown and can be edited on the screen. Each follicular puncture is stored as one record in the database file (IVF.DBF), no secondary files are used.

For the statistics option the user is first prompted to enter the beginning and the end of the time period to be examined. After the necessary computations a submenu asks whether general statistics or pregnancy statistics are to be shown. A hard copy of the statistics can easily be obtained with the print-screen command. Tables 2 and 3 show the screen displays of the variables calculated with the statistics program.

Comment

The first question to be asked in every database application is: which information should be stored? We decided it would be more reasonable to limit the database to a small number of pertinent variables to ensure that data are complete and to make best use of the possibilities of a personal computer. Our menu driven database system is simple, easy to use and can easily be modified and adapted to particular needs. The on-line computation of various statistical variables such as cleavage rate and pregnancy rate is a major advantage of our database system and permits constant quality control of the IVF programme.

Note

The minimum requirements for the database system are an IBM-PC or compatible with 128 K RAM, one disk drive, colour or monochrome monitor, and PC-DOS 2·0 and dBase II version 2·4 or higher. The program supports colour. A complete listing of the program files IVF.PRG (main menu), IVFENTER.PRG (enter oocyte retrieval), IVFGRAV.PRG (enter pregnancy), IVFMODI.PRG (modify record), IVFSTAT.PRG (statistics menu), IVFSTAT1.PRG (define time period to be examined), IVFSTAT2.PRG (general statistics), and IVFSTAT3.PRG (pregnancy statistics) is available from the authors upon request. The authors will copy the program files and the

Table 2. Screen display of general statistics (all numbers shown are fictitious)

```
                              IVF—STATISTIC
==========================================================================
           TIME PERIOD EXAMINED: FROM 84/01/01 TO 84/12/31
==========================================================================
Oocyte retrievals                          127
Embryo transfers (ET)                       80     % of retr      66·66
Pregnancies (excl biochemicals)             15     % of ET        18·75
--------------------------------------------------------------------------
Failed oocyte retrievals                     7     % of retr       5·51
Oocytes per retrieval            3·18  Oocytes retrieved          382
                                       Oocytes fertilized         160
Embryos per transfer             2·00  % Fertilized               41·88
--------------------------------------------------------------------------
PRESS ANY KEY TO RETURN TO STATISTICS MENU
WAITING
```

Table 3. Screen display of pregnancy statistics (all numbers shown are ficticious)

```
                         PREGNANCY—STATISTIC
           TIME PERIOD EXAMINED: FROM 84/01/01 TO 84/12/31
==========================================================================
   Embryos transferred        N            Pregnant        Pregnancy rate
--------------------------------------------------------------------------
          1                  31               4               12·9 %
          2                  28               4               14·2 %
          3                  14               5               35·7 %
         >3                   7               2               28 5 %
Total                        80              15               18.75%
--------------------------------------------------------------------------
   Outcome of pregnancy                N              % of pregnancies
--------------------------------------------------------------------------
Early abortion                         5                   33·3%
Late abortion                          2                   13·3%
Ectopic                                1                    6·6%
Birth                                  6                   40·0%
Not specified                          1                    6·6%
Total                                 15                  100·0%
--------------------------------------------------------------------------
PRESS ANY KEY TO RETURN TO STATISTICS MENU
WAITING
```

structure of the database file if a formatted disk is sent to them.

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The antenatal diagnosis by ultrasonography of type III congenital cystic adenomatoid malformation of the lung. Case report

S. F. MORCOS, M. O. LOBB

Case report

A 22-year-old woman had her first pregnancy terminated at 8 weeks gestation in 1980, she was booked in her second pregnancy in January 1985 at 15 weeks gestation.

A routine ultrasound examination at 18 weeks gestation by dates revealed a live fetus. The biparietal diameter and the femur length were consistent with a pregnancy of 18 weeks. The fetal lungs were very echogenic and enlarged, resulting in compression of the heart, downward displacement of the diaphragm, dilatation of the superior vena cava, and ascitis. No other abnormalities were recognized (Figs 1 and 2).

Type III cystic adenomatoid malformation of the lung was suspected and confirmed by fetoscopy and fetal lung biopsy at King's College Hospital.

The pregnancy was terminated with prostaglandin. Post-mortem examination of the 251 g-fetus revealed a protruberant abdomen but no other external abnormalities. Internal dissection showed all organ systems except the thoracic contents normally developed; there was a moderate quantity of ascitic fluid but no pleural effusion. On opening the chest, the lungs were very large and obscured the heart (Fig. 3).

The larynx and trachea appeared normal. After formalin fixation the volume of the right lung was 4·5 × 2·5 × 2 cm and the volume of the left lung was 4 × 2 × 2 cm. On slicing there was a firm, dull white/grey cut surface with no visible cystic spaces. This appearance was uniform throughout the lungs.

Histological examination of the lungs revealed type III adenomatoid malformation of the lung as defined by Stocker *et al.* (1977) (Figs 4 and 5).

Discussion

Congenital cystic adenomatoid malformation of the lung (CCAML) is a rare form of lung disease which was first described by Ch'in & Tang (1949). There were fewer than 200 cases of CCAML reported in the literature up to 1984. CCAML has been divided into three types by Stocker *et al.* (1975); the rarest is type 3 and we have found reports of only seven cases (Stocker *et al.* 1977; Miller *et al.* 1980; Oster & Fortune 1978; Diwan *et al.* 1983; Johnson *et al.* 1983; Cave & Adam 1984).

The antenatal ultrasound finding of type I CCAML has been reported by others (Garrett *et al.* 1975; Donn *et al.* 1981). Type III CCAML in only one lung has been reported (Diwan *et al.* 1983; Cave & Adam 1984). Our case is the first reported case where there was type III CCAML with bilateral total involvement of the lungs.

The echogenic appearance and bilateral total involvement of the lungs with dense cystic mass on ultrasound examination established the diagnosis which was confirmed by fetoscopy and fetal lung biopsy. The ultrasound examination delineated the extent of CCAML. Type I CCAML may give an ultrasound appearance similar to a diaphragmatic hernia.

Fewer than 200 cases of cystic adenomatoid malformation of the lung have been reported in the literature. The lesion most frequently affects one lobe and remains unilateral with almost equal frequency in all lobes. Bilateral involvement has been reported only twice before (Ch'in & Tang 1949; Oster & Fortune 1978).

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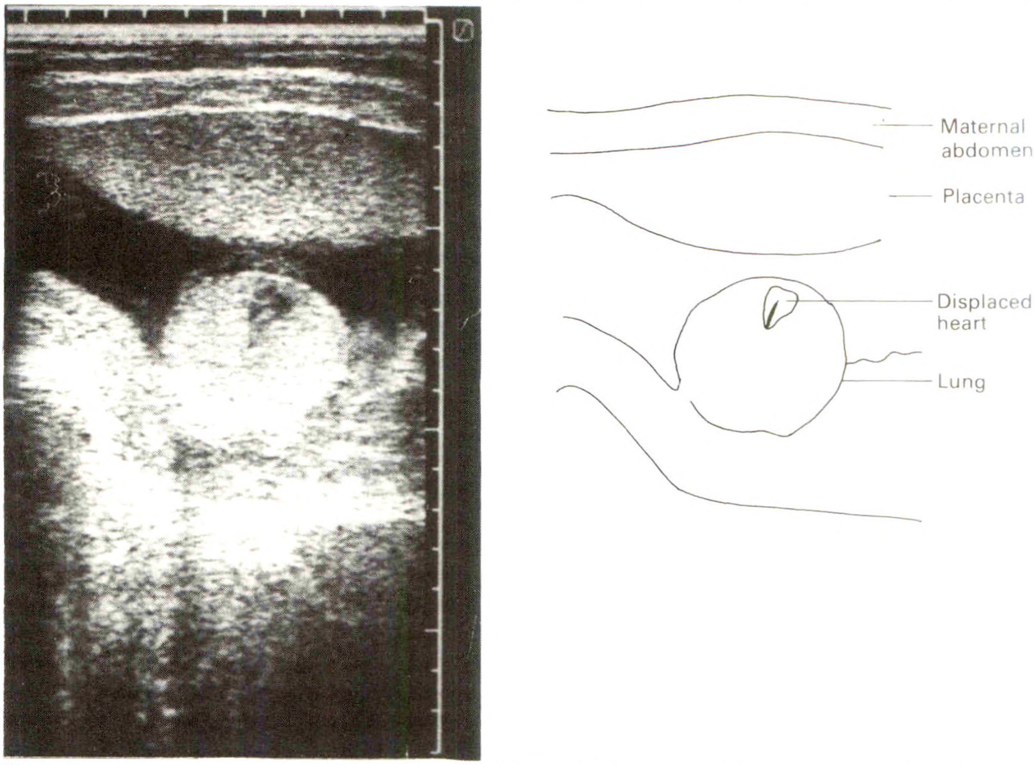

Fig. 1. Transverse section of fetal lungs and diagram. Note the similar ultrasound appearance between lungs and placenta.

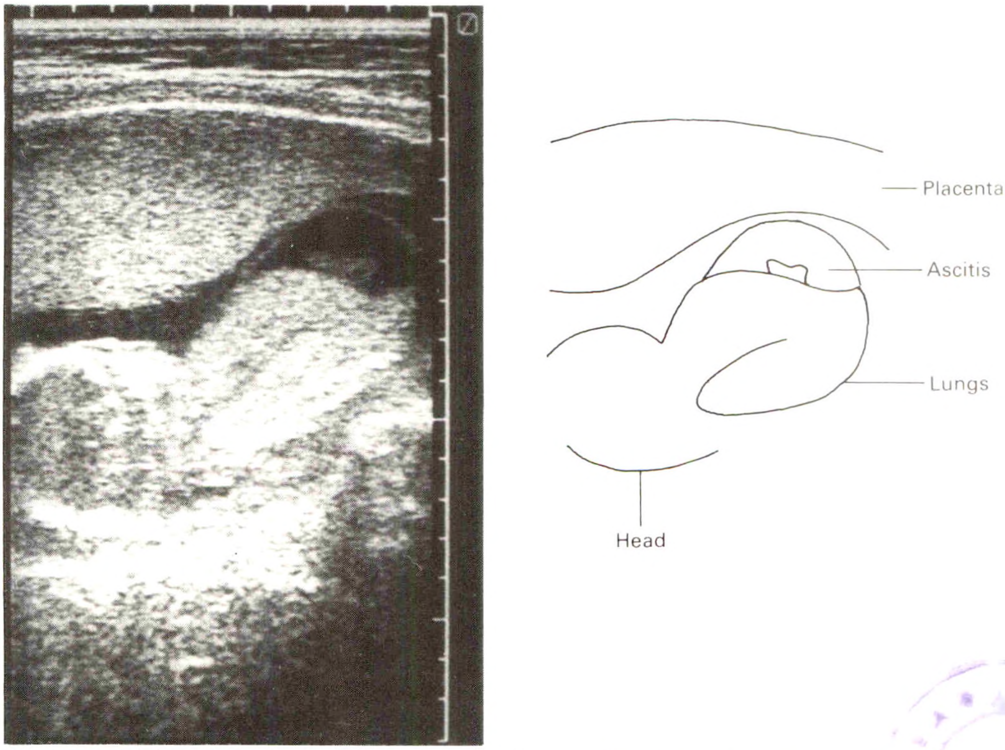

Fig. 2. Longitudinal section of the fetus and diagram showing echogenic lung appearance and ascitis.

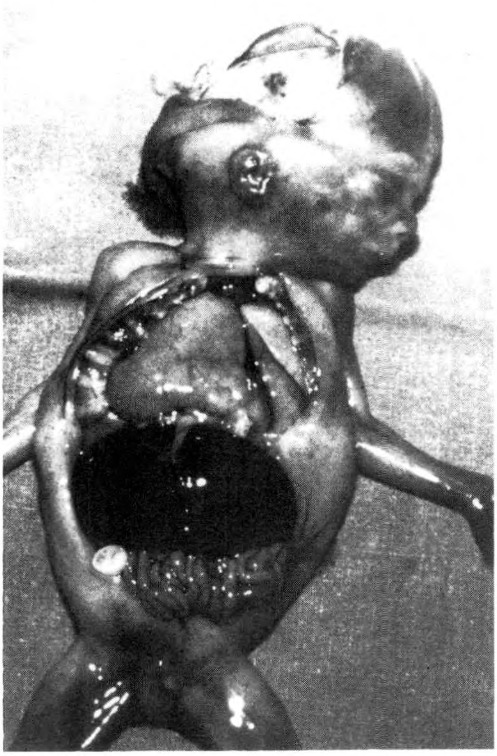

Fig. 3. Photograph of the fetus.

The affected lung tissue is characterized microscopically by numerous cystic spaces that are lined by bronchiolar epithelium and gland-like spaces or alveolar spaces that are lined by simple cuboidal or columnar epithelium with occasional mucin production.

The pathogenisis of CCAML remain unclear. The lesion has been considered to be a hamartoma (Van Dijk & Wagenvoort 1973); as a focal type of pulmonary dysplasia (Leninger & Haight 1973); and more recently a development anomaly (Oslon & Mendelsohn 1978).

The associated abnormalities with CCAML are maternal hydramnios, anasarca, prematurity, Potter's syndrome and jejunal atresia (Gerald & Merenstein 1969).

Three patterns of clinical presentation of CCAML have been reported. Firstly, stillbirth or neonatal death frequently associated with anasarca, prematurity and maternal polyhydramnios. Secondly, acute progressive respiratory distress in the newborn, and thirdly a more indolent course characterized by pulmonary infection.

In cases where the lesion affects one lobe or

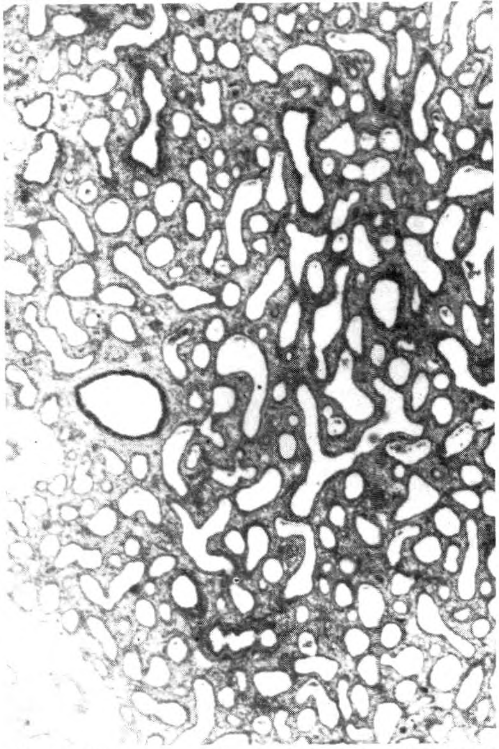

Fig. 4. Characteristic histological picture of CCAML type III, haematoxylin and eosin ×100.

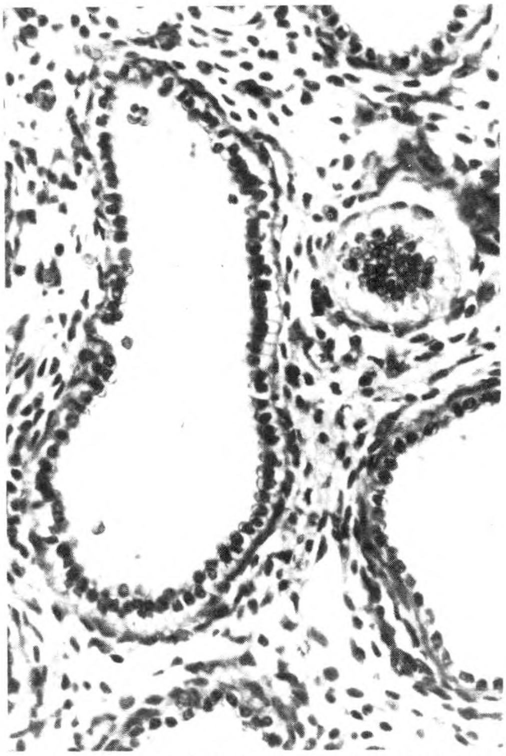

Fig. 5. Characteristic histological picture of CCAML type III, haematoxylin and eosin ×416.

one lung, the patient should be transferred before labour to a centre with neonatal surgical facilities so that surgical resection in the immediate postnatal period is possible and permit salvage of an otherwise normal child. Lobectomy and even pneumonectomy have been reported to be well tolerated in the neonatal period (Manson 1962; Halloran *et al.* 1972; Stauffer *et al.* 1984).

In cases where there is bilateral involvement of the lung termination of pregnancy should be recommended as so far the mortality rate has been 100%.

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Erratum

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Books received some of which may be reviewed at a later date.

Line 1, for **'Pregnancy Care. A Manual For Practice . . .'** read **'Prepregnancy Care. A Manual For Practice . . .'**.

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The course and outcome of pregnancy associated with bronchiectasis. Case report

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Case report

A 21-year-old patient, gravida 1, was admitted at 25 weeks gestation to the high-risk obstetric unit because of severe respiratory insufficiency. She was known to suffer from bronchiectasis and was being followed regularly by the department of medicine. No adverse aetiological factor was found, but her brother and one uncle also suffered from bronchiectasis. Before pregnancy her arterial blood gases were: Po_2 = 71 mmHg, Pco_2 = 33 mmHg, and pH = 7·43.

On admission, the patient appeared cachectic, weighing 45 kg. Physical examination revealed peripheral cyanosis, clubbing, tachypnoea (28 breaths/min), tachycardia (138 beats/min) and blood pressure of 130/80 mmHg. Diffuse ronchi and rales were present over both lungs, but breath sounds were not diminished. The uterus was small, with fundal height of 20 cm. Frequent bouts of severe productive cough were observed.

Laboratory studies revealed a haemoglobin concentration of 11·6 g/dl, WBC count 3300/μl albumin concentration 2·6 g/dl and globulin concentration 4·9 g/dl. Arterial Po_2 was 53 mmHg (on room air); Pco_2 was 35 mmHg; pH was 7·45, and bicarbonate was 47 mEq/l. Pulmonary function tests revealed a severe restrictive lung disease (Table 1). The electrocardiogram, apart from sinus tachycardia, was normal. An ultrasound showed both the biparietal diameter (BPD) and the femur length to be about the 50th centile, but abdominal circumference was less than the 10th centile for the relevant gestational age.

During her stay in the hospital, the patient was given a high-calorie/protein-rich diet (70 cal/kg/day). Respiratory physiotherapy, including terbutaline inhalations, was instituted daily. Oxygen was administered continually through a nasal catheter at a rate of 2·5 l/min. Despite these treatments, arterial blood oxygen tension remained between 50 and 70 mmHg. Arterial Pco_2 levels were moderately elevated, with metabolic correction of the respiratory acidosis (Table 2). On several occasions, there were bouts of fever, which were related to local bronchial infections. With each infective episode, the patient was given a course of amoxicillin and recovered rapidly. During infection, a deterioration in blood gas values was observed (Table 2).

The patient was not able to lie down, but had to sit up in bed so as to prevent a severe shortness of breath. Her ability to undertake even the mildest physical exertion was severely limited.

The pattern of asymmetrical growth retardation with head sparing, as determined ultrasonographically, persisted until labour (Table 3). However, the growth rate of both BPD and femur length diminished toward the third trimester, so that by 32 weeks these measurements were in the 10–25th centile range (Table 3). Amniotic fluid was within normal limits. Repeated fetal monitoring, using the non-stress

Table 1. Pulmonary function test at 25 weeks gestation, showing a severe restrictive disorder

	Predicted	Measured	% predicted
FVC (l)	4·1	1·9	47
FEV_1 (l)	3·3	1·2	36
FEV_1/FVC (%)	>75	62·8	—
MMEFR, 25–75% (l/s)	3·8	0·5	14

FVC, Forced vital capacity, FEV_1, forced expiratory volume in 1 s, MMEFR, maximal mid-expiratory flow rate

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Table 2. Arterial blood gases before, during and following pregnancy

Gestation (weeks)	P_{O_2}	P_{CO_2}	pH	Bicarbonate	BD	Respiratory environment
Before pregnancy	71	33	7·43	22	−2	Room air
25	53	35	7·49	27	3	Room air
28	52	39	7·44	26	2	Room air
30 (during infection)	53	'58	7·43	39	11	33% O_2
32	78	44	7·42	21·5	3	33% O_2
33 (intrapartum)	70	37	7·46	26	2·5	33% O_2
Postpartum	50	47	7·42	—	—	Room air
36 h postpartum	32	42	—	—	4	Room air

BD, base deficit

test and daily fetal movement count, was normal throughout gestation.

At 33 weeks gestation, 9 weeks after admission and while an elective induction was being contemplated, the patient went into spontaneous labour. Three hours later she was delivered of a male baby weighing 1650 g. Labour and delivery were uneventful, and FHR monitoring was normal. One- and 5-min Apgar scores were 9 and 10, respectively.

Within 12 h of delivery, the patient developed acute respiratory insufficiency accompanied by severe tachypnoea and cyanosis. Arterial P_{O_2} dropped to 32 mmHg (Table 2). There was no evidence of pneumonia on chest X-ray, and the differential white blood count was normal. Following 48 h of intensive respiratory support, including intermittent positive-pressure breathing, a moderate improvement was achieved. Two days later the patient was discharged, but had to continue intermittent oxygen therapy daily.

Discussion

A case of bronchiectasis during pregnancy in a young patient is described. Pulmonary function was impaired throughout gestation, as was demonstrated by a decrease in forced vital capacity (FVC), in forced expiratory volume (FEV), in maximal mid-expiratory flow rate and in FEV/FVC ratio. No improvement was obtained after salbutamol inhalation.

The striking feature in this case was the deterioration in the patient's respiratory status, particularly from 25 weeks onward. Hypoxaemia, hypercapnoea, recurrent bronchial infections, dyspnoea and exhaustion predominated.

Intrauterine growth retardation of the asymmetrical type was evident as early as 25 weeks gestation. This most likely reflects maternal hypoxaemia. The rate of growth of both the head and the femur were initially normal, but at 30 weeks started to decline, signifying the loss of head-sparing effect secondary to fetal hypoxaemia.

Table 3. Ultrasonic measures of fetal growth at different gestational ages

Gestation (weeks)	BPD (mm)	AC (mm)	FL (mm)	Estimated FW (g)	Normal FW (50th centile) (g)
16	32	—	—	—	—
23	52	—	39	—	—
25	64	19	45	733	811
27	69	21	50	900	1074
29·4	73	22·5	51	1094	1477
31·4	77	25.5	59	1438	1814
32·4	80	27·9	60	1700	2245

BPD, Biparietal diameter; AC, abdominal circumference; FL, femur length, FW, fetal weight

Most reports in the literature claim a much better prognosis for both the mother and the fetus. Teirstein (1965) reported a total of 44 pregnancies in 21 patients with bronchiectasis. In only one instance could difficulty during pregnancy or the postpartum period be attributed to this disease. Howie & Milne (1978) found little change in pulmonary function, degree of dyspnoea or volume of sputum production in each of three pregnant women with bronchiectasis, and no evidence of intrauterine growth retardation was observed. Templeton (1977) reported a patient with bronchiectasis and prior lobectomy, whose pregnancies resulted in an infant of low birthweight and an intrauterine fetal death at 38 weeks. However, the patient tolerated pregnancy well, and the only abnormality detected was maternal hypoxaemia.

Our results suggest that bronchiectasis can have an adverse effect on both the pregnant woman and her fetus. Close prenatal care with frequent assessment of pulmonary function, including blood gas analysis, good respiratory care and antibiotic treatment with the first signs of infection are essential. Prolonged bed rest and a high-calorie diet are also recommended. Regular ultrasonographic examinations from early pregnancy and fetal surveillance using biophysical tests should also be conducted. If maternal hypoxaemia is detected, particularly when signs of fetal growth retardation appear, we recommend early induction of labour.

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Tuberculous peritonitis in pregnancy. Case report

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Case report

A 25-year-old West Indian woman presented at 10 weeks gestation in her fourth pregnancy in apparent good health. She had had three normal term deliveries in the previous 7 years. In view of a close family history of pulmonary tuberculosis she had been under long-term observation by the local chest clinic. She had received BCG 2 years before this pregnancy and her chest X-ray had been normal 18 months later. During laparotomy, for a haemorrhagic corpus luteum, 16 months before conception, no peritoneal abnormality had been found. At 33 weeks the patient was admitted from the antenatal clinic with loss of weight (5 kg in 2 weeks), lassitude, nausea and vomiting.

Examination revealed an ill woman weighing 62 kg with a swinging pyrexia (36·0°–40·2°C), a maternal pulse of 100/min and blood pressure of 100/70 mmHg. The abdomen felt boggy to palpation, with a fundal height equivalent to the menstrual dates. Investigation showed a haemoglobin of 9·2 g/dl and a white cell count of 7·2 × 10^9/l. A chest X-ray on admission was unremarkable but the abdominal view suggested early small bowel obstruction.

Signs suggestive of septic shock developed 24 h after admission; maternal pulse 132/min, blood pressure 90/60 mmHg, temperature 35·2°C. Blood cultures were taken and the patient was moved to the intensive care unit where she was started on broad spectrum antibiotics and parenteral nutrition. Paracentesis, under ultrasound control, yielded straw coloured fluid with 550 WBC/ml (60% lymphocytes) but with no acid-fast bacilli seen on Ziehl–Neelsen's stain. Bone marrow examination was unhelpful. At 72 h when the rectal temperature had fallen to 32·4°C and episodes of marked fetal bradycardia had been noted on cardiotocography, a decision was made to deliver the patient by caesarean section.

The abdomen was opened through a mid-line incision and a large volume of cold viscous straw coloured fluid was found. The omentum was matted to small bowel. Extensive peritoneal tubercles allowed a clinical diagnosis of tuberculous peritonitis to be made. Access to the lower segment was impossible and a classical caesarean section was therefore performed. A live hypotonic male infant of 1·94 kg (50th centile) was born with a rectal temperature of 32°C and poor respiratory effort. His progress was satisfactory after the temperature became normal. Prophylactic treatment with isoniazid and pyridoxine was started and at 37 weeks by dates, BCG was given.

The mother remained in the intensive care unit for 3 weeks where antituberculosis treatment (streptomycin, rifampicin and isoniazid) was started and parenteral nutrition continued. Although repeated synacthen tests were normal the patient required reducing quantities of hydrocortisone for 10 days in order to maintain an adequate systolic blood pressure. Following an initial 14 stormy days the patient made a good physical recovery, although for several weeks she exhibited bizarre behaviour patterns which included rejection of the baby and aggression toward medical staff. With the baby weighing 3·42 kg she was discharged at 7 weeks.

Culture of biopsies of omental and peritoneal tubercles proved positive for acid-fast bacilli whilst ascitic fluid, sputums, urines, CSF and bone marrow were negative. The bacilli were fully sensitive to isoniazid, rifampicin and streptomycin.

At a 2 months' review, the mother was well and bottle-feeding a thriving infant. Pelvic examination revealed an involuted uterus fixed to a non-specific mass rising out of the pelvis. A barrier form of contraception was advised although it is probable that she is now sterile.

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Follow-up in the chest clinic over a 12-month period revealed no further evidence of active tuberculosis.

Discussion

Pulmonary tuberculosis complicating pregnancy is well-recognized (Snider 1984) but acute tuberculous peritonitis in pregnancy is not recorded in the published literature. Most of the recently reported series of acute tuberculous peritonitis (Gilinsky *et al.* 1983; Vyravanathan & Jeyarajah 1980; Lambrianides *et al.* 1980) include women of reproductive age but none was found to be pregnant. Several authors emphasized the importance of considering the diagnosis of acute tuberculous peritonitis in an acute abdomen with unusual features but the diagnosis is rarely made before laparotomy in the UK (Lambrianides *et al.* 1980).

Tuberculous peritonitis and pelvic tuberculosis are generally associated with infertility, but Snaith & Barns (1962) reported a 6% spontaneous pregnancy rate in women following antituberculous antibiotic therapy of proven pelvic tuberculosis. There was a high incidence of ectopic gestation, early pregnancy loss and intrauterine death in their series

Despite a strong family history of pulmonary tuberculosis, the diagnosis of tuberculous peritonitis was not made until the abdomen was opened and the very cold viscous ascites associated with the widespread tubercles were demonstrated. Laparotomy allowed correct diagnosis and birth of a live infant. The response to antituberculous therapy after delivery was excellent, and the patient's Addisonian-like state resolved spontaneously over 2 weeks.

Laboratory confirmation of the diagnosis may only come weeks later, with the culture results. In the acutely ill patient, the diagnosis which may only be a clinical suspicion, must be confirmed by laparotomy, with associated delivery of the baby and institution of the correct antituberculous therapy.

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Abdominal pregnancy complicated by appendicitis. Case report

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Case report

A 24-year-old Asian woman was admitted at 11 weeks gestation in her first pregnancy complaining of severe continuous lower abdominal pain for 24 h. There was no vaginal bleeding. She had noticed intermittent lower abdominal pain for 4 weeks previously and had received ampicillin from her general practitioner for a presumed urinary tract infection. She had felt feverish for about 1 week.

Her history included a laparotomy at the age of 8 years. The reason was not clear, but extensive peritoneal adhesions had been reported. A diagnosis of tuberculosis had been made and she was treated with streptomycin, *p*-aminosalicylic acid and isoniazid.

Nine months before admission she had been admitted with symptoms suggestive of intestinal obstruction. This episode settled with conservative management.

At the present admissions she was obviously in pain. She was apyrexial and not clinically anaemic. General examination was unremarkable but abdominal examination revealed tenderness suprapubically and in the right iliac fossa, with some rebound tenderness. No masses were felt. Pelvic examination confirmed generalized pelvic tenderness and a bulky uterus.

The haemoglobin was 12·5 g/dl and the white cell count was $11{\cdot}6\times10^9/l$ (90·6% neutrophils). An ESR was 30 mm/h. Urea, electrolytes and liver function tests were all normal. An ultrasound scan was reported as showing a viable pregnancy, of 11 weeks gestation, lying within the uterus. It was also reported that there was a fibroid in the anterior uterine wall.

Surgical advice was sought, but no conclusive diagnosis was made and the patient, whose condition was now settling, was observed. After 2 days her temperature rose to 37·8°C but her general condition remained satisfactory. Her haemoglobin was 11·9 g/dl and her white cell count had risen to $19{\cdot}3\times10^9/l$ (89·8% neutrophils). Urinary examination failed to show any signs of bacterial infection.

Suddenly, whilst resting in bed, her condition worsened with increased abdominal pain and signs of peritonitis. Laparotomy was performed after initial resuscitative measures, and on entering the peritoneal cavity one litre of fresh blood was found. A fetus (crown-rump length of 45 mm) was found floating freely in the pelvis. The placenta and sac were attached to the right pelvic side wall and pouch of Douglas. An infected appendix mass, involving the right fallopian tube and ovary loosely and overlying the remains of the pregnancy, was dissected free and removed. The damage to the right fallopian tube and ovary was such that right salpingo-oophorectomy was required to achieve haemostasis. After removal of the remnants of the pregnancy, haemostasis was found to be adequate. A few adhesions were found in the peritoneal cavity from bowel to parietal peritoneum in the left flank and the left fallopian tube exhibited signs of past infection, being slightly convoluted and bound down to the posterior aspect of the left broad ligament by flimsy adhesions.

Three units of blood were transfused and she was given cefuroxime 750 mg 8-hourly and metronidazole 500 mg 8-hourly intravenously. Her postoperative recovery was uneventful and the patient was discharged from hospital afer 9 days. Histological examination confirmed acute suppurative appendicitis, products of conception and the right fallopian tube and ovary showing

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reactive serosal inflammation. Histology failed to show any trophoblastic invasion of the appendix, fallopian tube or ovary.

Discussion

Abdominocyesis is a comparatively rare complication of pregnancy with a quoted rate of 1 in 1955 (Zuspan *et al.* 1957) and 1 in 5000 pregnancies (King 1954). Overall a wide range of rates have been reported from 1 in 286 to 1 in 15 000 (Zuspan *et al.* 1957). The literature, however, is well supplied with reports of abdominal pregnancies. The first reported abdominal pregnancy was described by Abulcasis in the 10th century, who observed the discharge of fetal parts through the abdominal wall in the umbilical region; further umbilical fistulae discharging fetal parts were described in the 16th century by Cornax in 1545, Felix Platter in 1584, and Jacob Noierus in 1595 (King 1954).

More recently abdominal pregnancies have been reported presenting as splenomegaly (Dasadhikary *et al.* 1979), associated with intestinal obstruction (Chatterjee *et al.* 1975), and with renal and genital tuberculosis with haemolytic anaemia (Semchyshyn & Cecutti 1975).

Appendicitis is also not a common complication of pregnancy. In a series of 42 936 deliveries between 1945 and 1964, Brant (1967) reported 24 cases of proven appendicitis giving a rate of 1 in 1789 deliveries (0·06%).

Abdominal pregnancies may be classified into primary or secondary depending on the location of nidation. The first reported case of primary abdominal pregnancy was described by Galabin in 1896 (Studdiford 1942; Cavanagh 1958). The criteria described by Studdiford (1942) to establish a diagnosis of primary abdominal pregnancy require (i) both tubes and ovaries to be normal with no evidence of recent or remote injury, (ii) the absence of any evidence of uteroperitoneal fistula, and (iii) the presence of a pregnancy related exclusively to the peritoneal surface and early enough to eliminate the possibility of secondary implantation following primary nidation in the tube. Clearly, in our patient, the presence of infection in the region of the right tube and the evidence of past infection in the left tube do not allow the diagnosis of primary abdominal pregnancy.

The diagnosis of ectopic gestation was not made until laparotomy, reassurance of a viable intrauterine pregnancy having been obtained by the ultrasound scan. In retrospect the reported anterior wall fibroid was no less than the entire uterus, with the pregnancy lying in the pouch of Douglas. The absolute diagnosis of an ectopic pregnancy by ultrasound scanning is an uncommon event (Robinson & de Crespigny 1983).

In our patient the abdominal pregnancy underwent spontaneous disruption whilst in close proximity to an acutely inflammed appendix, giving rise to the acute condition after 2 days of observation, as a consequence of intraperitoneal haemorrhage rather than rupture of the appendix mass, which, although containing quantities of pus, was found to be intact at laparotomy.

A search of the literature had failed to find a similar case report.

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Fulminant hepatic failure associated with aplastic anaemia after treatment with danazol. Case report

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Case report

A 29-year-old woman was admitted to Hamamatsu University Hospital on 21 September 1983, because of jaundice and a skin eruption. She had no history of liver disease. She had been suffering from dysmenorrhoea due to endometriosis for several years and had received hormone therapy including androgens and progestogens. Baldy-Webster's operation was performed in 1982. Dysmenorrhoea recurred in 1983 and treatment with danazol (Sterling-Winthrop Research Institute, New York), 400 mg/day, was started on 8 September 1983. On 17 September she began to complain of fatigue, anorexia and nausea and she had a skin rash on her trunk and extremities. On 19 September she visited a local doctor because of the rash and jaundice. Investigation revealed hepatic dysfunction with total bilirubin 6·4 mg/dl (109 µmol/l), glutamate-oxaloacetate transaminase (GOT) 2118 units (normal values <30), glutamate-pyruvate transaminase (GPT) 2094 units (normal <20). Danazol was stopped and she was referred to Hamamatsu University Hospital on 21 September. On admission, she was a well-nourished and well-orientated woman. There was marked jaundice and generalized erythema which was strongly suggestive of toxic dermatitis. The liver was soft, tender and was palpable 2 cm below the costal margin. The spleen was not palpable. There was no ascites and no neurological abnormality.

Laboratory investigations showed the following values: red blood cell count, 5·76×10^6/µl, white blood cell count, 6900/µl, platelet count 26·5×10^4/µl, GOT 1510 units, GPT 1572 units, lactate dehydrogenase 1026 units (normal <350), total bilirubin 28·0 mg/dl (48 µmol/l), conjugated bilirubin 19·0 mg/dl, albumin 3·6 g/dl, γ-globulin 0·8 g/dl, α-fetoprotein 29 ng/ml (normal <20), prothrombin time 25%. Hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody and hepatitis A antibody (IgM) were not detected

Deterioration of liver function tests continued after admission (Fig. 1). Total bilirubin level rose to 32·6 mg/dl (56 µmol/l), and prothrombin time fell to 8% on 29 September. On 30 September, she became delirious and disorientated and an electroencephalogram showed slow waves and triphasic waves. Fulminant hepatic failure was diagnosed and daily plasma exchange, using 3 litre of fresh plasma, was initiated. Consciousness as well as hepatic function improved remarkably after five consecutive plasma exchanges and she had completely recovered from hepatic coma by 7 October.

However, her serum bilirubin and transaminases began to increase again after the plasma exchange and hepatic coma of grade III had returned by the end of October. Plasma exchange was resumed, this time in combination with prednisolone (60 mg/day), and the hepatic coma disappeared and the liver function tests also improved. She was considered to have recovered from fulminant hepatic failure by 26 January 1984 when laparoscopy and liver biopsy was performed. The liver was soft and slightly

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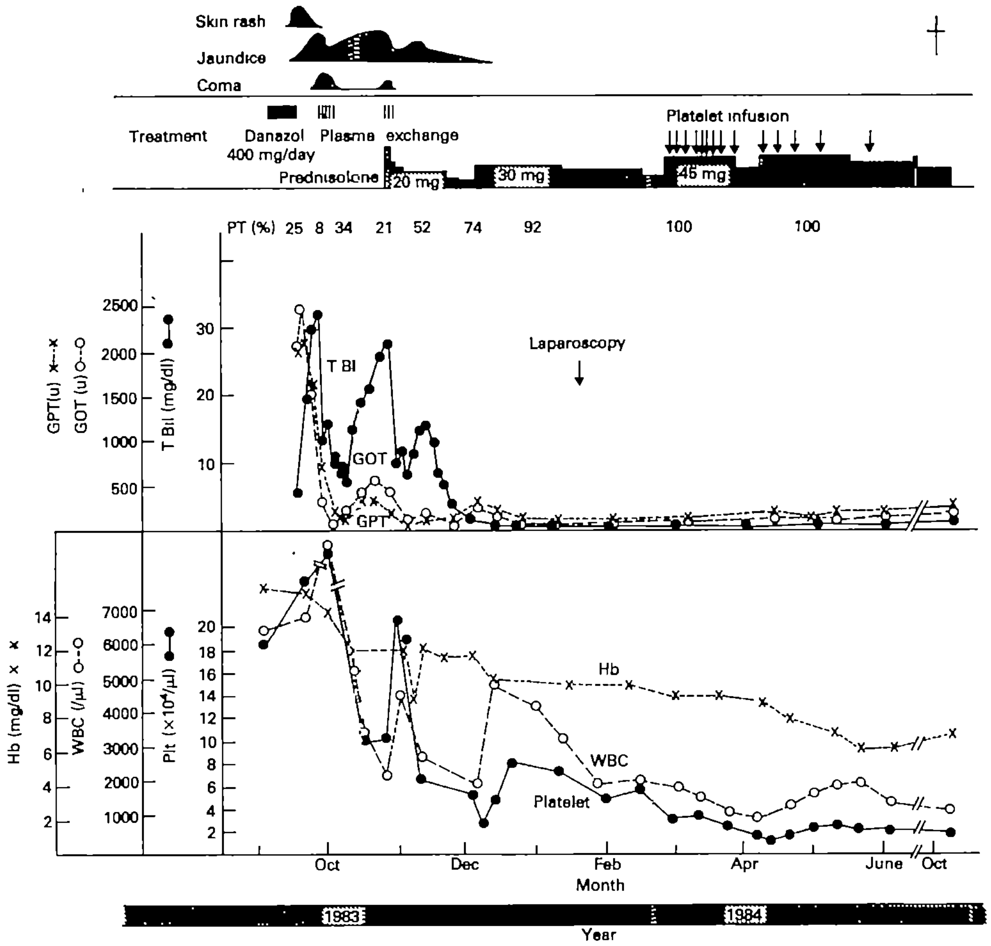

Fig. 1. Clinical course of the patient.

enlarged and histological examination showed regeneration of hepatocytes with marginal mononuclear cell infiltration in the portal area compatible with the stage of recovery from acute hepatitis.

A decrease in platelet count became evident at the beginning of November 1983. At that time anti-platelet antibody was not detected and the bone marrow was normal. It was assumed that the thrombocytopenia was due to the marked splenomegaly associated with the fulminant hepatitis. Thrombocytopenia, leukopenia and then pancytopenia returned in February 1984. Bone marrow obtained by sternal puncture on 28 March was fatty and extremely hypoplastic and aplastic anaemia was diagnosed, she did not respond to treatment and died on 22 October 1984 because of bleeding and pneumonia.

Discussion

This is the first report of a patient with fulminant hepatic failure related to danazol treatment. Danazol, 2,3,isoxazol derivative of 17α-ethinyle testosterone, is a synthetic steroid with anti-gonadotrophin activity and is commonly used in the treatment of endometriosis (Rannevik 1979), benign breast disease (Dmowski 1979) and idiopathic angioneurotic oedema (Hosea *et al.* 1980). Recently, the effect of this drug on idiopathic thrombocytopenic purpura has also been mentioned (Ahn *et al.* 1983).

Among the side-effects of danazol, acne, weight gain and hirsutism are ascribed to the androgenic nature of this drug (Dmowski 1979; Rannevik 1979). With its structure of 17α-alkylated anabolic steroid, danazol might induce hepatic dysfunction (Adlercreutz & Tenhunen 1970; Pearson & Zimmerman 1980). Recently, there have been reports of increased levels of transaminases after danazol therapy but the reported hepatic dysfunction associated with danazol was always mild (Pearson & Zimmerman 1980; Vincens *et al.* 1984) and serious hepatotoxicity has not been described previously.

In our patient, there are several reasons for believe that danazol was responsible for the hepatic failure. (i) Toxic dermatitis appeared at the same time as the hepatic dysfunction. (ii) Danazol was the only drug employed. (iii) Fatal hepatic injuries due to 17α-alkylated anabolic steroids have been described previously (Goldon *et al.* 1960; Wilder 1962). (iv) The patient's lymphocytes incubated with danazol showed increased incorporation of ^{3}H-thymidine into DNA (data not shown) which would indicate the sensitization of lymphocytes against danazol (Holland & Mauer 1964). (v) Serological markers of hepatitis A and hepatitis B viruses were not detected. These findings strongly suggest that danazol was the aetiologic agent in both toxic dermatitis and liver damage in this patient, although we cannot completely exclude the possibility of acute non-A, non-B hepatitis.

Severe aplastic anaemia was associated with acute hepatic failure in our patient. It seems unlikely that danazol was directly responsible for the bone marrow suppression, since anabolic steroids have been widely used in the treatment of aplastic anaemia, and there have been no reports of aplastic anaemia associated with anabolic steroid therapy including danazol. Our patient appears to be an example of 'hepatitis-aplastic anaemia syndrome' (Hagler *et al.* 1975; Watananukul *et al.* 1977), in which aplastic anaemia occurs after recovery from hepatitis. More than 200 patients with this syndrome have been reported (Zeldis *et al.* 1983).

We conclude that fulminant hepatic failure in this patient was an unusual effect of danazol and aplastic anaemia was a consequence of hepatic injury.

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CORRESPONDENCE

An audit of the detection and management of small-for-gestational age babies

Dear Sir,

Hepburn & Rosenberg [*Br J Obstet Gynaecol* (1986) **93,** 212–216] are mistaken when they say that antenatal detection of intrauterine growth retardation made little difference to the outcome for the baby. In their group of 95 unsuspected cases of growth retardation, 17 (18%) of the infants were classified as 'ill'—that is, stillborn, or admitted to the special care baby unit for more than 48 h. In order to test the hypothesis in a randomized trial that antenatal detection of growth retardation would halve the proportion of ill babies from 18% to 9%, one would require 300 patients in each arm ($\alpha = 0{\cdot}05$; $\beta = 0{\cdot}10$) (Pocock 1983). It is therefore unlikely that a retrospective survey of 129 cases of growth retardation will show a significant difference in the number of ill babies, and the possibility remains that successful detection of growth retardation antenatally will reduce the number of ill babies.

Another criticism of this article is the use of the 10th centile in the diagnosis of growth retardation. Obstetricians realize that many infants with severe growth retardation due to utero-placental insufficiency have birthweights above the 10th centile, while some infants whose birthweights are below the 10th centile are small for genetic reasons and not because of utero-placental insufficiency. The 10th centile is convenient for epidemiologists when describing populations of small babies, but it is of little use to obstetricians, who are more concerned with poor fetal growth as a manifestation of utero-placental insufficiency, with its risk of stillbirth and intrapartum fetal hypoxia. The findings of this article would have been of much more value if other measurements of fetal growth had been made in the newborn, such as ponderal index (Miller & Hassanein 1971) and skin fold thickness (Oakley *et al.* 1977) in the assessment of whether growth retardation (that is utero-placental insufficiency) were present or not. The accuracy of diagnosing utero-placental insufficiency is of much more interest to obstetricians.

The authors are also wrong when they state that the management of this condition was unsatisfactory. It is encouraging that the most severe cases of growth retardation were diagnosed antenatally and delivered electively, and that of the 51 cases wrongly suspected of growth retardation, only one had an elective caesarean section. Hepburn and Rosenberg have not produced evidence of 'unsatisfactory management' of growth retardation in this study: on the contrary I think the hospital under review managed its cases well.

This study illustrates many of the disadvantages of small retrospective surveys. While such an audit is of interest to the hospital from which the information is derived, and would be suitable for a lunch-time perinatal meeting, it only adds confusion to an already difficult subject. It may even be harmful, for it seems to imply that there is little point in obstetricians even trying to detect intrauterine growth retardation antenatally

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Author's reply

Dear Sir,

We agree with Dr Grant on the preferability of randomized trials over retrospective reviews and did so in the concluding statement of our paper—'the priority would appear to be to concentrate on tests of fetal well-being rather than fetal size and to evaluate their effectiveness in controlled trials'. It is indeed possible that a trial such as he suggests to test the effect of antenatal detection of growth retardation might show some effect on morbidity and mortality. The practical difficulties of carrying out such a trial, however, are immense. Dr Grant has made several rather arbitrary choices for his calculation of sample sizes. Using the observed proportions of ill babies in the two groups (24% and 18%) and a more conservative Type II error ($\beta = 0{\cdot}05$), the required number of patients in each arm would be 1200. In order to recruit 1200 babies in the suspected group, given the pick-up rate of 26% of babies less than the 10th centile, it would be necessary to screen more than 46 000 women. Because of the impossibility of conducting such a trial one should not be so dismissive of the retrospective information which is available; the finding in our small sample that morbidity was similar in the suspected and unsuspected group is therefore still a worthwhile observation.

We also entirely agree that there is poor correlation between birthweight centile and fetal well-being and, indeed, this was the main conclusion of our paper. We pointed out that small size for gestational age has a heterogeneous aetiology and the majority of such babies are healthy. Since birthweight centile is, however, the criterion commonly used in obstetric practice, we made use of our data to demonstrate its inadequacy in identifying babies at risk and concluded, again as quoted above, that instead of concentrating on fetal weight for gestation there is a need to develop tests of well-being.

Dr Grant was incorrect when he stated that the most severe cases of growth retardation were suspected antenatally (rather inconsistently he defines growth retardation at this point according to birthweight centile). While the two babies electively delivered were the smallest for gestational age in the *suspected* group, there were equally small-for-gestational age babies in the unsuspected group. Indeed, Fig. 2 illustrates that there were 63 babies less than the fifth centile; of these only 19 (30%) were suspected.

Dr Grant underestimates the importance of intervention in the false positive group by concentrating on the single elective delivery at 35 weeks. There were, in addition, numerous investigations in 39 of the 51 women and seven admissions lasting from 1 to 6 weeks; the cost in terms of unnecessary anxiety and domestic disruption must be considered in addition to the financial costs at a time of economic stringency.

Dr Grant has clearly misunderstood our paper in his inference that obstetricians should stop attempting the antenatal diagnosis of growth retardation. Our point was that estimating fetal size for gestation is an inappropriate way of doing this. Finally, he states that these results are of limited local value; their agreement, however, with results from two other specialist hospitals (including his own) suggests a more widespread relevance (Hall *et al.* 1980; Rosenberg *et al.* 1982).

Our aim in presenting these aggregate data was not to pass judgement on clinical management by individual clinicians but to provide an overview of the efficacy, in practice, of current diagnostic procedures and to indicate where the problems lie.

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Uterine activity in the second stage of labour and the effect of epidural analgesia

Dear Sir,

Bates *et al.* [*Br J Obstet Gynaecol* (1985) **92**, 1246–1250] have demonstrated objectively what many have believed for some time; that epidural analgesia reduces the uterine expulsive forces in the second stage of labour. Understanding and acceptance of this simple fact should help to reduce the increase in instrumental deliveries associated with epidural analgesia which has been reported by many authors. We believe that ignorance of the ideal management of epidural analgesia combined with slavish adherence to arbitrary time limits has been much more responsible for the increased instrumental

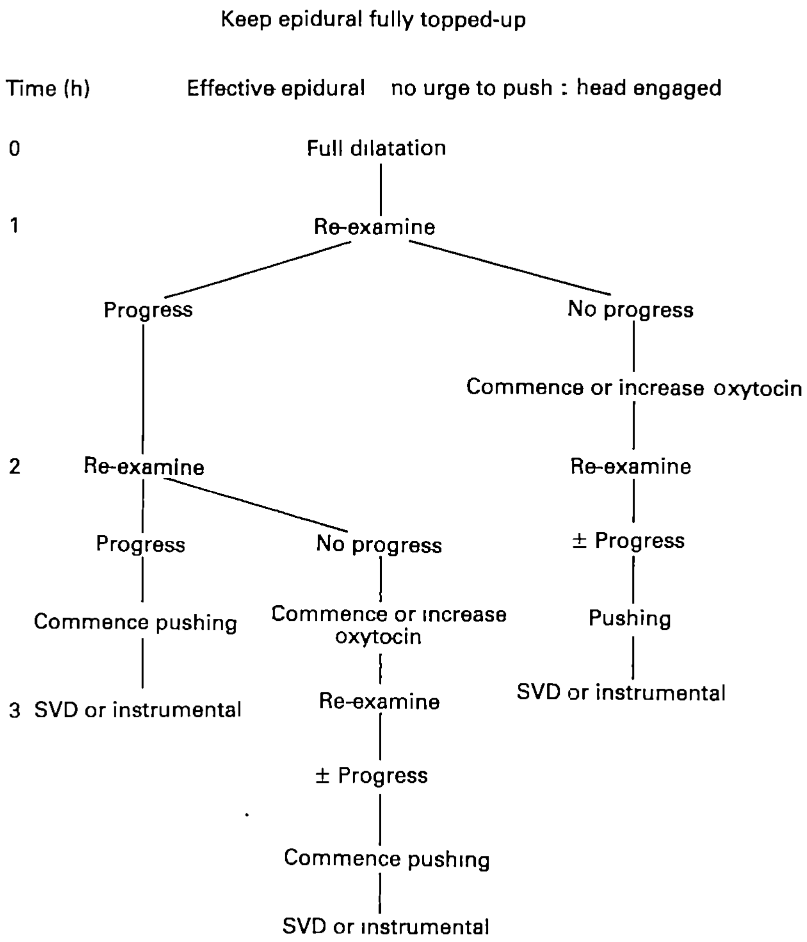

Fig. 1. Guide lines for management of the second stage under epidural analgesia. SVD, Spontaneous vaginal delivery.

deliveries than any reduction in uterine expulsive powers. Following an increase in our forceps delivery rate in those patients with epidural analgesia and singleton pregnancy (our overall forceps rate being 7·5%) in 1985 we have introduced the following guidelines for the management of the second stage under epidural analgesia (Fig. 1). We are confident that with experience comparable forceps rates with and without epidural analgesia can be achieved.

The paper by Bates *et al.* (1985) should provide a stimulus to all who manage labour under epidural analgesia to question the validity of their management protocols.

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BOOK REVIEWS

Gynaecologic Oncology edited by Robert C. Knapp & Ross C. Berkowitz. Macmillan Publishing Company, New York, 1986, 658 pages with figures and tables, $65.00

At a time when sub-specialization is rapidly developing throughout the World, gynaecological oncology, probably the easiest defined of all sub specialties is seeing a rapid proliferation of new text books. One of the latest offerings by Robert Knapp and Ross Berkowitz is an attempt to bring together an overview of basic sciences related to this multidisciplinary subject, together with clinical management and the complexity of complications and related disorders which may follow treatment.

The book is expensively produced on excellent quality paper but surprisingly has extremely bad photomicrographs of poor quality and minute size. Many of the drawings have been taken from other publications, therefore there is a loss of uniformity throughout the text. Other illustrations particular of clinical material and surprisingly photographs of histological material are unwarrantably poor.

In the areas of clinical management the chapter on carcinoma of the vulva tends to be rather old-fashioned with many older references and in particular has some very tiny photographs of poor quality. A similar comment can be made about the chapters on carcinoma of the vagina and the fallopian tube.

It is also unfortunate that for a text which should be looking for a worldwide market that the vast majority of references are American with very rare reference to authors from elsewhere.

The presentation makes reading easy and the chapters by the two editors are of very high quality. Unfortunately one's overall impression of the text is that it has probably been a long time in the making and there are a significant number of areas which already need revision. The chapter on the management of cervical malignancies is probably the best in the whole text. It exhaustively covers the diagnosis and management, including all the problems of determining the most appropriate treatment, and then finally completes the picture by dealing with rare tumours of the cervix and the management of pregnancy problems. This chapter is extremely well referenced and can be used as an important information source.

Overall this is a good book which attempts to cover in its four units the basic science aspect of cancer, the sites affected, problems of complications and the supportive care of the cancer patient. The concept is excellent but is seriously hampered by old references and amazingly poor illustrations.

J. M. Monaghan

The Management of Labour edited by John Studd. Blackwell Scientific Publications, Oxford, 1985, 380 pages with figures and tables, £27.50

John Studd has once again displayed his talent for identifying an area in need of his editorial abilities and has met it by selecting expert contributors who write well. The result is a splendid volume which is destined to become a standard reference for anyone interested in intrapartum care. Friedman's classic monograph 'Labour: Clinical Evaluation and Management' has filled this role for the past two decades but at last we have a major volume on labour published on this side of the Atlantic which is free of the problems imposed by the need to distil the real message from the mists of North American language and clinical practice. The book is fairly comprehensive; it deals fully with the physiology and clinical control of the uterus, fetus and neonate and there are sensitive sections addressing the wider emotional needs and comfort of the mother.

One neglected area may be the management of mothers with major clinical problems in labour, such as severe hypertension, diabetes, cardiac disease and anaemia. That apart, it is an excellent addition to the shelves. Inevitably, it reflects some of the prejudices and obsessions of the editor but one could never accuse Studd of being dull, least of all in his preface, which sets the mood for what is to follow. 'It is all to common for self-appointed experts to emerge years after they have retired from frontline obstetrics . . . to appear in a witness box creating future policies by a legal judgment that will be more persuasive and more durable than the finest clinical research'. These first words of the preface demonstrate the editor's ability to score a direct hit and this accuracy and relevance is maintained for most of the 350 or so pages of this excellent addition to the literature on intrapartum care.

A. A. Calder

Risks of Labour (Perinatal Practice Volume 2) Edited by J. W. Crawford. John Wiley & Sons, Chichester, 1985, 214 pages with figures and tables, £29.50

This book is the second in a series entitled 'Perinatal Practice' organized by Geoffrey Chamberlain and Forrester Cockburn and in it Jack Crawford has got together a group of authors with a wealth of expertise and experience. The contributors come both from the obstetric and paediatric sides of perinatology and the sum total is a comprehensive source of valuable information concerning the causes and effects of intrapartum morbidity. The results is a highly informative source of information which provides the paediatrician with an insight into some of the obstetrician's difficulties and dilemmas and gives the obstetrician an insight into the problems of the damaged neonate and those who are called on to care for him. Of particular value among the latter are the four chapters which deal with various aspects of cerebral damage and dysfunction. The editor, as well as contributing a thoughtful and sensitive chapter on maternal trauma, has producted a very worthwhile volume which would be an asset to the library of any maternity hospital.

A. A. Calder

Clinical Gynaecological Oncology edited by John H. Shepherd & John M. Monaghan. Blackwell Scientific Publications, Oxford, 1985, 422 pages with figures and tables, £32.50

The evolution of sub-specialization within obstetrics and gynaecology has quite naturally provided the stimulus and created the need for texts such as this not only to provide baseline data for those wishing to embark on a sub-specialized career but also to keep all in the specialty informed and aware of developments.

This book, edited by two internationally acknowledged and respected gynaecological oncologists, presents contributions from a wide range of oncological experts who have attempted to crystallize and clarify the essence of current knowledge in their own fields.

The format is initially traditional beginning with epidemiology, continuing with chapters on pre-invasive disease of the lower genital tract and then dealing with invasive cancers with individual chapters by tumour site. In this early part of the book the emphasis is heavily biased toward surgical oncology with both editors making a major contribution in this area. There are two specialized pathology sections one dealing comprehensively with intra-epithelial neoplasia and the other with epithelial ovarian malignancy. The latter half of the text is more orientated toward specific areas of management including chemotherapy and radiotherapy. A useful inclusion is that of chapters concerned with supportive therapy (nutrition, intensive care and septic shock) and terminal care, the latter a welcome and important inclusion. Gestational trophoblastic disease, cancer complicating pregnancy and malignant gynaecological disease in childhood are also covered.

The standard and clarity of presentation is, on the whole, excellent with efficient use of understandable tables and clear figures. Most authors concisely covered their chosen subjects and areas of uncertainty and controversy were highlighted by abundant reference material. Most of the contributors avoided too much self-opinionation, presenting and summarizing but allowing the reader to assess currently available data. There were exceptions however. On the treatment of carcinoma of the endometrium, fractional curettage and hysteroscopy are advocated as investigative techniques, and adjuvant chemotherapy whole pelvic irradiation is suggested for patients with positive peritoneal cytology; neither would represent the consensus in the UK. The section on trophoblastic disease, while clear concise and practically very useful concentrates on the Charing Cross experience, it could only be enhanced by the inclusion of and comparison with data from other centres.

Some of the chapters dealing with rarer tumours (Fallopian tube) or rare situations (Cancer in pregnancy) are understandably descriptive and based on collective anecdote.

The section on radiotherapy in gynaecological oncology over-emphasizes the technical aspects of treatment. It is a difficult task to cover all aspects of management in a single chapter and perhaps the large amount of data presented might have been more clearly summarized, the non-radiotherapist might be somewhat confused by this section.

Although the book has covered most aspects of gynaecological malignancy, some reference to the design, conduct and analysis of clinical trials would have been useful. Likewise the role of reconstructive surgery would have been a welcome addition.

Gynaecological oncology is a rapidly maturing and changing sub-speciality and any textbook automatically suffers from 'premature ageing', no doubt, the necessity for further editions has already been considered by the editors. On their first edition they are to be congratulated. I believe that many specialized and non-specialized gynaecologists and colleagues in related disciplines will find much of value in this book.

David Luesley

Antenatal Care Assessed (A Case Study of an Innovation in Aberdeen) by Marion Hall, Sally Macintyre & Maureen Porter. The Aberdeen University Press Ltd., Aberdeen, 1985, 144 pages with figures and tables, £12.50

Screening large populations offers the possibility or preventing certain adverse events but it is important to recognize that screening itself may actually cause harm. Nowhere are the problems of assessment of benefits and hazards more obvious than in the field of antenatal care—and yet no complete systematic evaluation has yet taken place. Aberdeen is in the forefront in questionning the efficiency and timing of the components of antenatal care, and this book reports the results of a study which attempted to introduce a new rationalized scheme of care to the city

Readers will recall the publications of Chng, Hall and MacGillivray some 5 years ago, analysing the results of a detailed case note study of Aberdeen primiparae and showing firstly how few risk factors were taken into account by obstetricians and secondly how few abnormalities were identified at any one antenatal visit. This resulted in Marion Hall suggesting that there should be fewer antenatal visits and that it would be more appropriate for general practitioners to undertake more of the care

This study therefore reports the attempts to change the policy and habits of all those involved in obstetric care and monitor the results in terms not only of obstetric outcome but also in terms of the acceptability to obstetricians, general practitioners, midwives and mothers themselves.

The results make fascinating reading, and show the enormous difficulty in obtaining co-operation for change. Interestingly the midwives had attended meetings to discuss the various changes and co-operated fully, many obstetricians lacked the interest to attend meetings but complained at the decisions that had been made, and only 19% of general practitioners fully augmented the design. It was therefore impossible to assess the whole scheme but was possible to compare mothers for whom the design had been implemented with those whose care followed the previous and more traditional pattern. Interestingly, the mothers with the new form of care actually disliked the relatively long intervals between visits. The reasons given were the need for more frequent reassurance and advice on symptoms or problems. Mothers seemed happier with their visits to general practitioners' surgeries than to hospitals. Conversely, however, a case note study showed that diagnoses such as breech presentation or small-for-dates were made much more accurately in the hospital, especially if the examining clinician was of registrar or senior registrar status.

The authors have performed a valuable service in showing in detail the complexity of assesssing the medical value of antenatal examinations combined with medical value of antenatal examinations combined with the social and psychological components. This book should be read by all involved in antenatal care. An added bonus for those purchasing it is a delightful Lowry picture on the dust jacket.

Jean Golding

Gynaecologic Cancer. A Clinicopathologic Approach edited by D. Cavanagh, E. H. Ruffolo & D. E. Marsden. Appleton-Century-Crofts, Norwalk, Connecticut, 1985, 359 pages with figures and tables, £56.95

The aim of the authors is to 'fulfil the need for a short text book which emphasizes the importance of clinicopathologic correlation in the area of gynecologic oncology'. By and large they have succeeded. The photomicrographs (black and white) are of excellent quality. The photographs of gross specimens are fewer in number and not so good. The quality of the chapters varies also.

In particular, those on cancer of the cervix, cancer of the endometrium and gestational trophoblastic neoplasia are exhaustive in presenting the state of the art. The chapter on primary non-epithelial ovarian cancer suffers from the stated aim of the authors in keeping the book 'short'. This chapter especially is rather fragmented and in places almost anecdotal. This is counteracted by the inclusion of a very extensive and up to date list of references.

The quality of the paper and the photomicrographs presumably account for the somewhat elevated price of this book. Nevertheless, it will act as a useful guide providing the pathologist with current thoughts in clinical practice and the clinician with histopathological details which may influence that practice and both with a modern bibliography.

Ian D. Duncan

Chemically Induced Birth Defects (Drugs and Chemical Toxicology Series Volume 2) by James L. Schardein. Marcel Dekker Inc, New York, 1985, 879 pages with figures and tables, $125.00 (US and Canada), $150.00 (all other countries)

Each book on this subject that I encounter is longer and heavier than the one before. This book is no exception: not only is it 879 pages long, the type is minute throughout. For those who like reading the small print, this book is for you. It is incredibly thoroughly researched: some chapters containing 600 or more reference, up to the year 1983. That one man has managed to distil so much information, is surely a remarkable achievement. It is more specialized than some of its predecessors, being primarily concerned with organogenesis, though behavioural teratology gets mention.

The introduction covers the principles of teratogenesis then 19 chapters deal with different classes of drugs and the remaining 12 with chemicals (pesticides, metals, solvents, dyes, food additives, pollutants, cosmetics, alcohol, tobacco etc). Each chapter has an orderly format which is easy to follow, with an introduction, an account of animal studies followed by human studies, for each sub-class of compounds (for example: narcotics, anti-gout and anti-inflammatory agents in the analgesic chapter). Much of the copious information has been sensibly tabulated, while the accounts of human and some animal work are somewhat gruesomely illustrated by photographs.

I have a few minor criticisms (just to show I read some of the text!). There is a slight tendency to cite, as if it were valid evidence, the odd isolated case report of a deformed fetus whose mother took a particular drug in early pregnancy. She may also have smoked, eaten curry and been given the evil eye by a witch. Who can say which factor was causative? The history of litigatious do-it-yourself teratology in America is littered with fallacious arguments (though of course Mr Schardein himself does not fall into these traps). There is a simple word game, allied to the board game called Mastermind, in which one player writes down a five-letter word in secret, and the second player has to divine it by suggesting successive words and being told how many letters they have in common with the original word. If told that 'style' has two letters correct and 'clean' also has two the illogician may look for features in common and so believe the correct letters to be 1 and e, whereas 'stack', in which neither is present, could also be the correct answer. So we may seek in vain for common causative factors, whereas many and various causes may combine in different pregnancies to provoke a single multifactorial birth defect.

Some preambles contain slightly banal pharmacology: 'Antihypertensives have as their primary function the lowering of systemic arterial (blood) pressure', and dopamine is classed as an antihypertensive. But these are minor quibbles. The whole is a remarkable work, which will probably prove the most complete readily available reference book for some years to come.

Felicity Reynolds

Clinics in Obstetrics and Gynaecology Vol 12 No. 3. Reproductive Endocrinology edited by Howard Jacobs. W. B. Saunders, Co., London, 1985, 531–751 pages with figures and tables, £13.75

Insofar as this issue of the popular series 'Clinics in Obstetrics and Gynaecology' has a central theme, it is the polycystic ovary syndrome. It is not encouraging that the editor misspells Leventhal in the foreward. Polycystic ovary syndrome is only a thread binding together some chapters. The rest ranges widely from male hypogonadism to nutrition and reproduction. The audience is therefore difficult to identify. It is likely to appeal to gynaecological endocrinologists with a main concern in infertility and has little interest for the trainee or established general gynaecologist.

The book is largely a production of the colleagues of Professor Howard Jacobs at the Middlesex Hospital and St Mary's Hospital. Nine out of the 18 authors of the 9 chapters hail from there. This gave the editor, Howard Jacobs, the advantage of close contact with his authors but restricted the list of contributors somewhat. A further criticism must be levelled, not at the editor and contributors, but at the publishers. They have presumably insisted on the house style of citing references by author and year and not by superscript numbers. It is difficult enough to read an original article which cites a moderate number of authors by name in the text: it becomes intolerable when you have to parse sentences in order to disentangle the meaning from the endless series of names. There are 148 references, many of which occur more than once, in 19 pages of text on hirsutism by David Morris. There cannot be more than a handful of people in the world who would appreciate or need that much and it makes it very difficult for the rest of use to read with any pleasure.

Two chapters in particular do justice to the polycystic ovary theme. Franks and his colleagues in their chapter on ovulatory disorders in women with polycystic ovary syndrome have written a useful up-to-date vade-mecum for clinicians who have to deal with this common disorder. Tan and Jacobs write a persuasive account of the use of ultrasound examination of the ovary in the diagnosis of amenorrhoea and give an authoritative guide to the use of pulsatile luteinizing hormone releasing hormone in clinical practice.

Arnold Klopper

Perinatal Medicine. Proceedings of the IX European Congress of Perinatal Medicine held in Dublin, September 1984 edited by J. Clinch & T. Matthews. MTP Press Ltd, Lancaster, Boston, 1985, 354 pages with figures and tables, £45.00

Books which are produced as records of the proceedings of international congresses often achieve little more than allowing the contributors an opportunity to publish their work with less effort and less peer review than is generally required. This volume which represents the proceedings of the IXth European Congress of Perinatal Medicine held in Dublin in September 1984 is different. Although it runs to a total of 55 chapters, to which can be added the pronouncements of the chairmen of the congress sessions, the book does achieve considerable success in covering many of the important aspects of modern perinatal medicine. Inevitably the quality of the contributions varies considerably but the editors are to be congratulated on a good finished product. While some of the contributions are rather on the short side, there is a nice mix of those based on the very best scientific data and those which might charitably be described as perinatal poetry so that there is something for everyone and the end result is an asset to the literature.

A. A. Calder

Intrauterine Contraception. Advances and Future Prospects. (Proceedings of an International Workshop on Intrauterine Contraception: Advances and Future Prospects, 1984) edited by G. I. Zatuchni, A. Goldsmith & J. J. Sciarra. Harper and Row Publishers, Philadelphia, London, 1985, 504 pages and figures and tables, £27.50

This is the product of an international workshop sponsored by the Program for Applied Research on Fertility Regulation (PARFR), in May 1984. PARFR has sponsored 12 other such workshops over more than a decade with the aim of bringing together experts from around the world to review and disseminate the findings of applied research in the field of fertility regulation and, hopefully identify the most promising directions for further research. The material in this volume is, not surprisingly, orientated towards the scientific and research communities. Readers whose interest is purely clinical would probably find that discussions about national experiences with intrauterine devices (IUDs), governmental and regulatory agencies, multicentre comparative clinical trials and the research and development of devices that will probably not become available to them, have little relevance to their everyday practice. Among the 'technical advances' presented uterine cavity measurement holds out hope of improving IUD performance by better matching of IUD and uterine dimensions but metrology devices such as the Wing Sound and Cavimeter have yet to be proved clinically useful. The value of ultrasound and X-rays in IUD management is indisputable. Their use and limitations and the potential advantages of vaginal application of the ultrasound probe are well presented (but the author is misguided in suggesting that 'almost all perforated IUDs are easily removed from the abdominal cavity by laparoscopy'). Uterine bleeding and pelvic inflammatory disease (PID), the old bugbears linked with IUDs, are revisited. If nothing else, readers are likely to be convinced how difficult it is to determine the true risk of PID specifically attributable to the use of IUDs. One fact seems certain: IUDs, unlike some other forms of contraception, do not protect the user against PID or its consequences. A causal relation is difficult to disprove and perhaps this will eventually lead to the IUDs' decline in some parts of the world, at least. An apparently unforeseen prospect at the time of the workshop was the manufacturer's decision to discontinue production of the Cu 7 and Cu T devices in the United States of America because the escalating cost of defending product litigation made continuing in the IUD business there no longer economically sensible. This volume is undoubtedly a major addition to the literature on intrauterine contraception but the ordinary gynaecologist or family planning doctor is unlikely to find it particularly valuable; only devoted followers of the state of the art would want to have it on their personal bookshelves.

R. P. Husemeyer

Prenatal and Perinatal Infections; report on a WHO meeting. (EURO Reports and Studies No. 93). World Health Organization Regional Office for Europe, Copenhagen, 147 pages Sw Fr 12

This small paperback handbook is useful as a short but up-to-date account of prenatal and perinatal infections, principally viral, although some bacterial, chlamydial and toxoplasma infections are discussed briefly It is well referenced, and contains some tables and figures.

Rosalinde Hurley

Books received some of which may be published at a later date

Perinatal Health Services in Europe edited by J. M. L. Phaff. Published on behalf of the World Health Organization, Regional Office for Europe by Croom Helm Ltd, Beckenham, 1986, 211 pages with figures and tables, £19.95

Primal Health. A Blueprint for Our Survival by Michael Odent. Century Hutchinson Ltd, London, 1986, 192 pages, £9.95

Manual of Gynaecology by Thankam R. Varma. Churchill Livingstone, Edinburgh, 1986, 348 pages with figures and tables, £11.95

Routine Cytological Staining Techniques. Theoretical Background and Practice by Mathilde E. Boon & Johanna S. Drijver. Macmillan Ltd, Basingstoke, 1986, 238 pages fully illustrated, hardback £25.00, paperback £10.95

Transsexualism and Sex Reassignment edited by William A. W. Walters & Michael W. Ross. Oxford University Press, Oxford, 1986, 191 pages with figures and tables, £17.50

Clinics in Anaesthesiology: Vol 4 No. 1 (two volumes) **Obstetric Analgesia and Anaesthesia I** (pages 1–232) and **Obstetric Analgesia and Anaesthesia II** (pages 233–444), edited by G. W. Ostheimer. W. B. Saunders Co., London, 1986, each volume £13.50

Infertility in the Male (Current Reviews in Obstetrics and Gynaecology) by Anne M. Jequier. Churchill Livingstone, Edinburgh, 1986, 154 pages with figures and tables, £18.00

Active Management of Labour Second Edition by Kieran O'Driscoll & Declan Meagher. Baillière Tindall, London, 1986, 204 pages with figures and tables, £9.95

Clinics in Obstetrics and Gynaecology. Volume 13 No. 1 Termination of Pregnancy edited by John J. Laferla. W. B. Saunders Co., London, 1986, 160 pages with figures and tables, £13.50

Environmental Health Criteria 55 Ethylene Oxide (IPCS International Programme on Chemical Safety). World Health Organization, Geneva, 1986, Sw Fr 9

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4th edition

Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates

Edited by **C. R. Whitfield,** MD, MB BCh, FRCP, FRCOG, Regius
Professor of Midwifery, University of Glasgow and
Honorary Consultant Obstetrician and Gynaecologist,
Queen Mother's Hospital and Western Infirmary, Glasgow
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Edited by Frank E. Hytten

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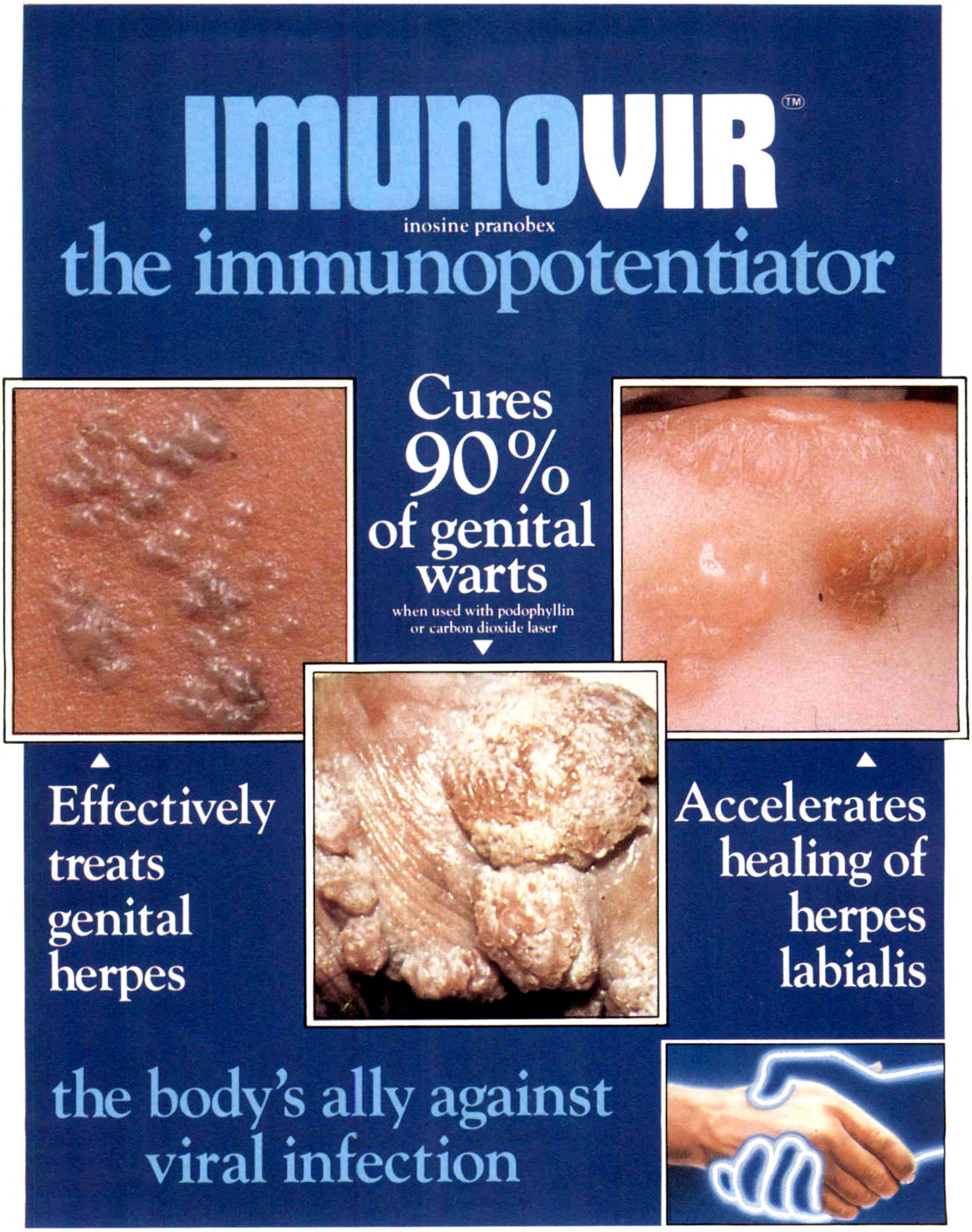
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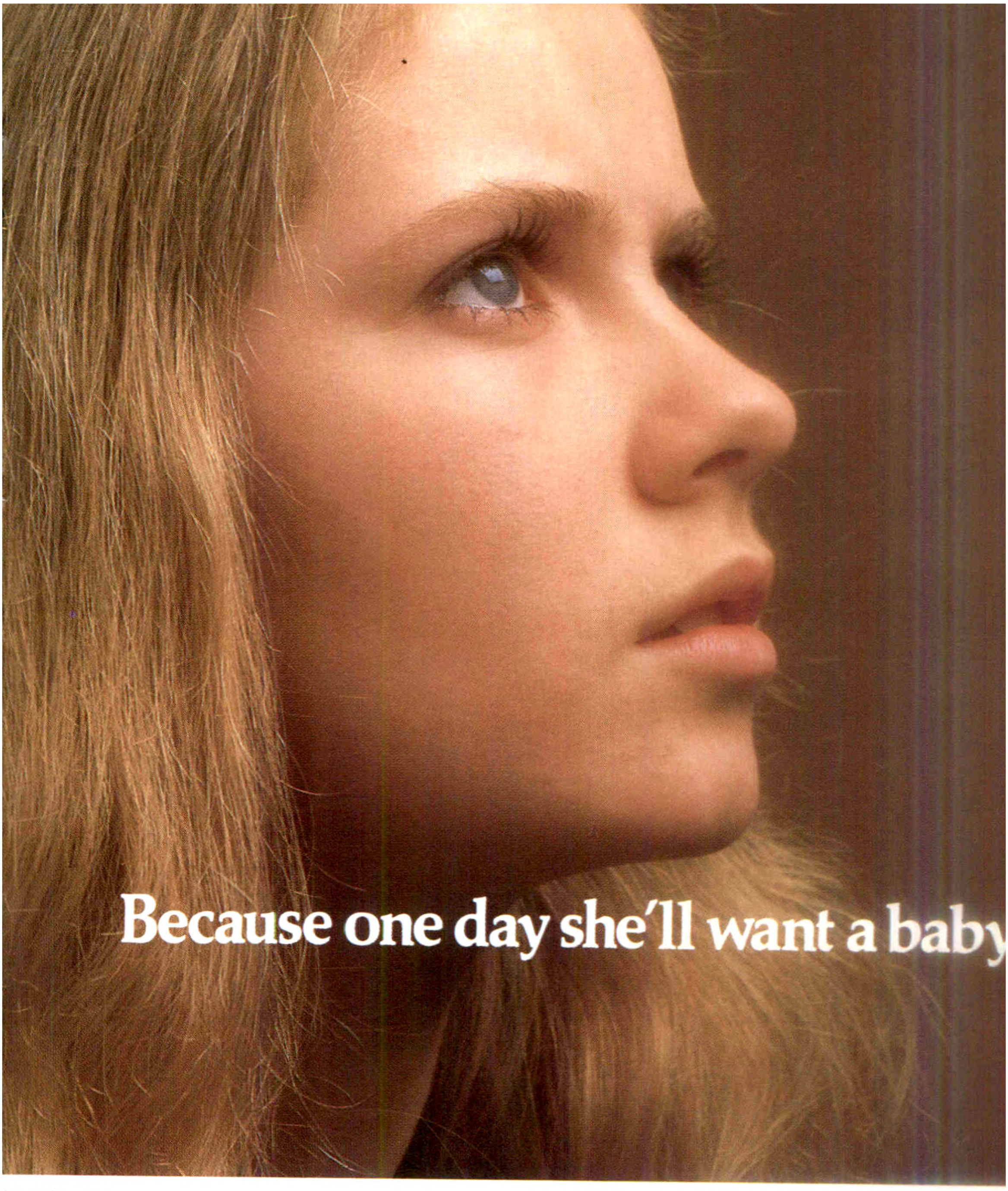
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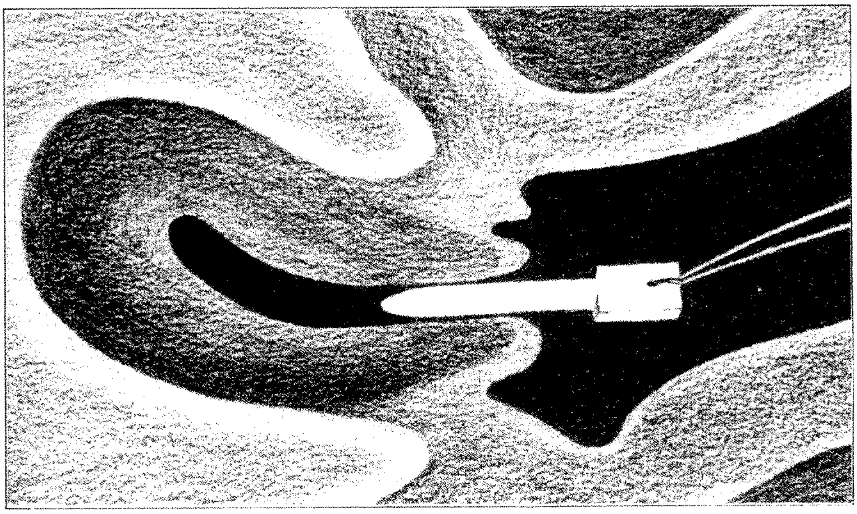

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TECHNICAL DATA OVERLEAF

TECHNICAL DATA

DATA SHEET

PDS* (Polydioxanone) Sterilised Monofilament Synthetic Absorbable Suture

Presentation
PDS (Polydioxanone) Monofilament Synthetic Absorbable Suture is prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding either D & C blue No 6 (gauges metric 0.2 and 0.3, 10/0 and 9/0) or D & C violet No 2 (gauges metric 0.4 to 5.0, 8/0 to 2) during polymerisation. These sutures may also be manufactured undyed (clear).

PDS (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Data obtained from implantation studies in rats show that, at two weeks post implantation, approximately 70% of the suture strength is retained whilst at four weeks the strength retention is approximately 50%. At eight weeks approximately 14% of the original strength remains. *This indicates a significantly longer period of wound support than previously available with an absorbable suture.*

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within six months.

Uses
PDS (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal epithelium sutures could cause localised irritation if left in place for longer than 10 days. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

The safety and effectiveness of PDS (Polydioxanone) sutures in neural and cardiac tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category P
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities
The gauge range initially available will be 0.2 metric (10/0) to 5 metric (2). Various lengths of material attached to non traumatic stainless steel needles are packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sale is 12 or 24 packs contained in a film wrapped drawer style carton.

Further Information
No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos 0508/0011 (dyed); 0508/0012 (clear).
Br Pat No 1 540 053.

Date of preparation of Data Sheet - September 1982
Revised 8/1986.

DATA SHEET

Coated VICRYL* (Polyglactin 910) Sterilised Braided Synthetic Absorbable Suture

Presentation
The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Sutures may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses
Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration
By implantation

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 7 days and should be removed as indicated.

At the discretion of the surgeon, appropriate non-absorbable sutures may be used to provide additional wound support when coated VICRYL sutures are used in ophthalmic procedures.

The safety and effectiveness of Coated VICRYL (polyglactin 910) Sutures in neural tissue and in cardiovascular tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category P
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities
Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sales is 12 packs contained in a film wrapped drawer style carton.

Further Information
No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence No 0508/0009
Br. Pat. No. 1583390

Date of Preparation of Data Sheet April 1981
Revised 8/1986

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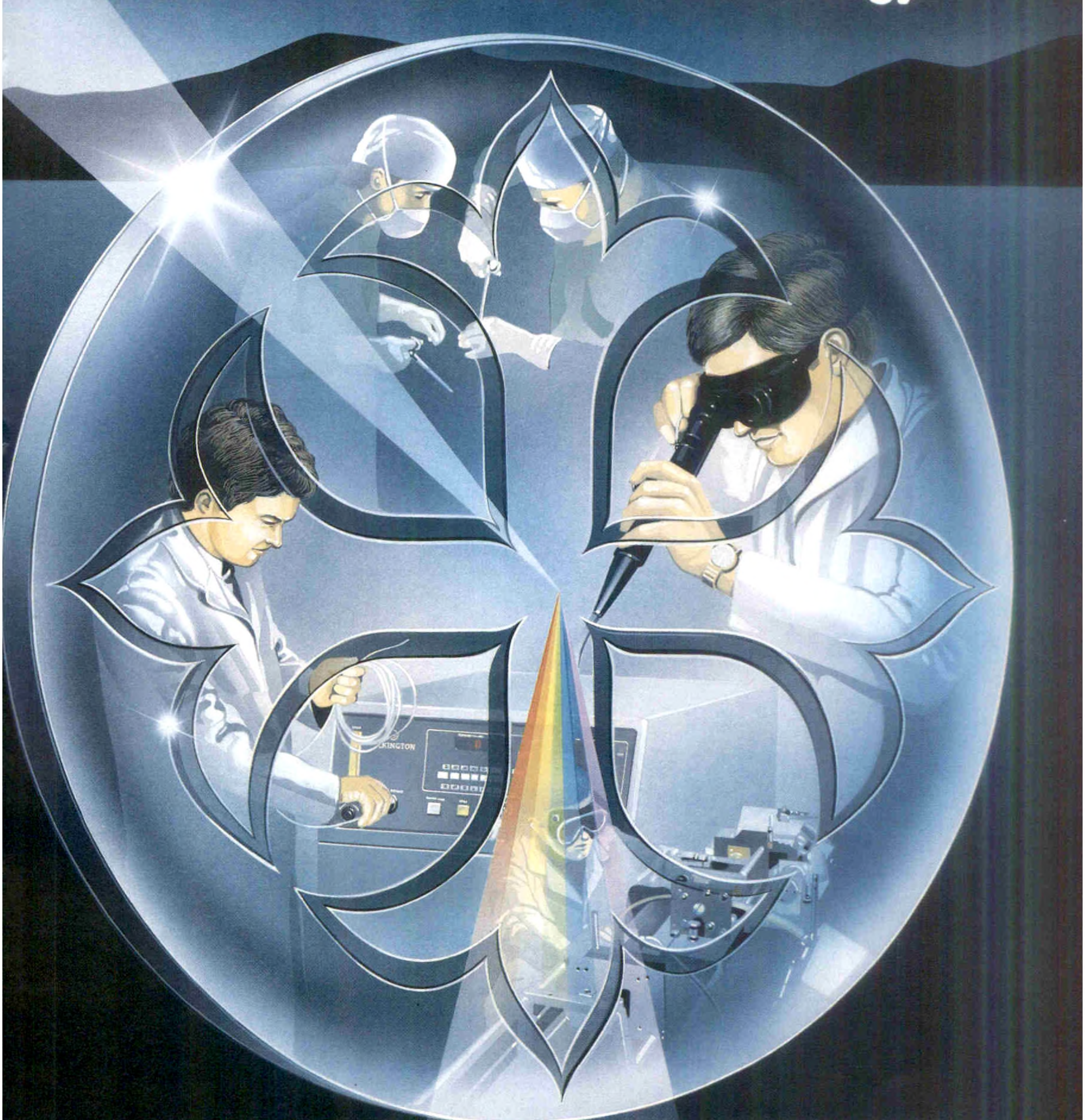

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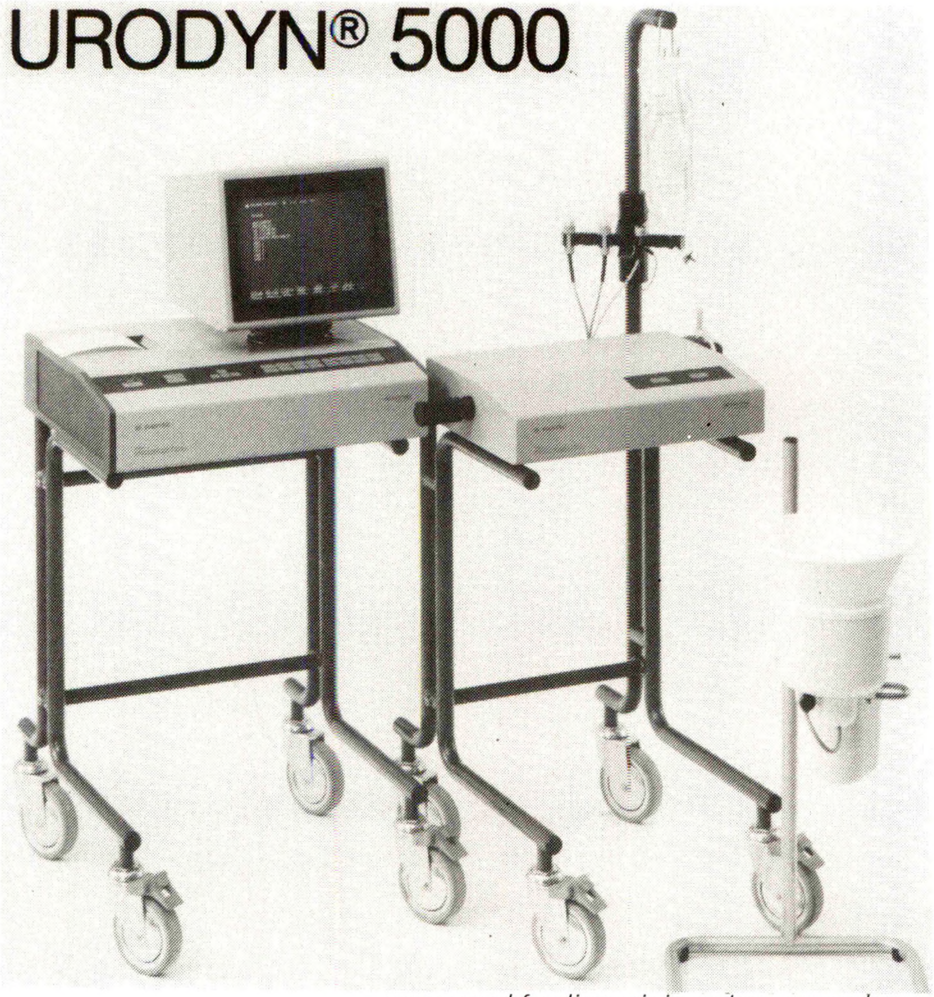

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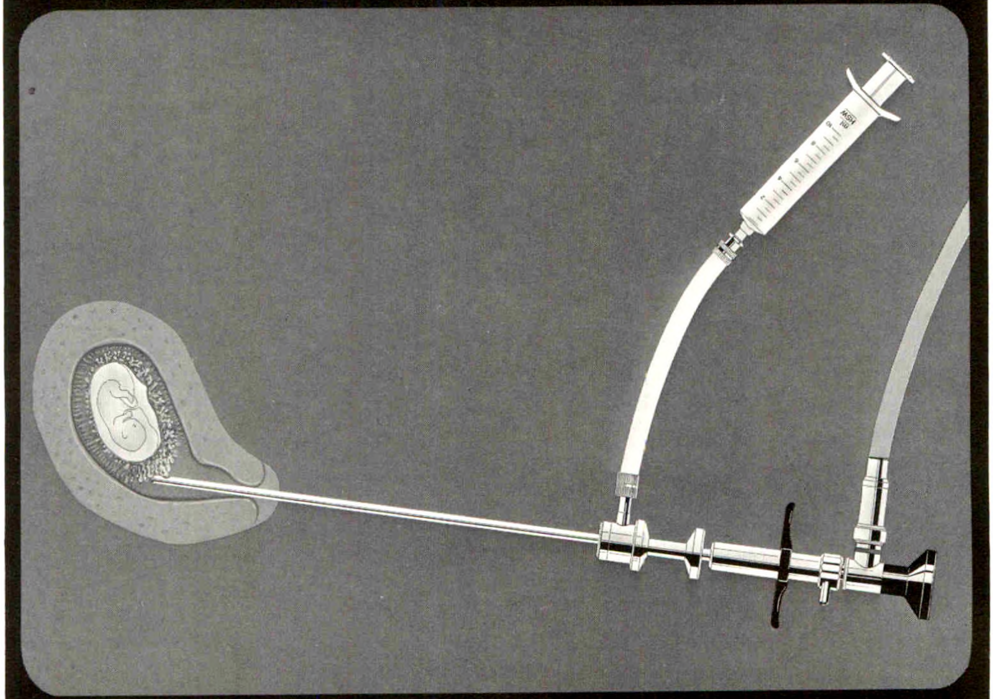

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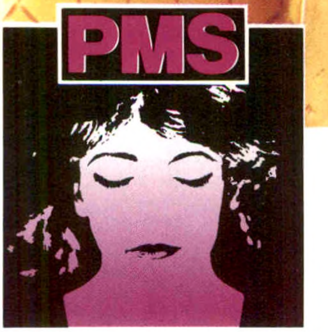

It has been estimated that every month in the over half a million women and girls have to time off work or school because of nenstrual problems[1]

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COMMENTARY

Management of prolactinomas—1986

At least one third of women with hyperprolactinaemia have a prolactinoma (Franks & Jacobs 1983) and whereas most are microadenomas (<10 mm in diameter), a few of the tumours are large and extend out of the pituitary fossa to compromise the optic chiasma or to compress or invade the cavernous sinus.

The therapeutic approaches presently available for patients with prolactinomas are medical treatment with dopamine agonists such as bromocriptine, selective pituitary surgery or radiotherapy. The major advance in the last decade has been the realization that treatment with bromocriptine not only suppresses hypersecretion of prolactin, but it may also result in shrinkage of the tumour, largely through reduction in the size of the tumour cells (Tindall *et al.* 1982). A number of reports have shown that treatment with bromocriptine can improve visual field defects and those using computerized tomography have confirmed tumour shrinkage (McGregor *et al.* 1979; Tan & Jacobs 1986). It has now been established that 90% of prolactinomas regress on treatment with bromocriptine (Bergh & Nillius 1982); even very large tumours with serum prolactin concentrations of 80 000–120 000 u/l (2000–3000 ng/ml) may show remarkable shrinkage (Velentzas *et al.* 1981). In cases where no shrinkage occurs despite suppression of prolactin secretion, the tumour is usually not a prolactinoma, but has caused secondary hyperprolactinaemia by compressing the pituitary stalk or hypothalamus.

The argument in favour of medical treatment is made more compelling by the results of long-term follow-up, an issue that we can now begin to address after a decade of use of bromocriptine (Tan & Jacobs 1985). At the present time the following conclusions can be drawn: (1) The clinical response to treatment with bromocriptine in women with hyperprolactinaemia and proven prolactinoma has been consistently favourable and is maintained during prolonged treatment. There have been no cumulative side-effects and no reports of tumour progression or growth of proven prolactinomas during treatment with bromocriptine (Corenblum & Taylor 1983). The maintenance dose of bromocriptine is usually much lower than the dose needed to induce remission and in our experience is about 5 mg/day. (2) When medication has been stopped after treatment for several years, although in many cases serum prolactin concentrations returned to pretreatment levels, in the majority there has been no regrowth of the tumour. In a recent report, for instance, 15 patients with prolactinomas were treated for 1·5–7 (mean 3·7) years: when the bromocriptine was withdrawn the tumour or gland size remained unchanged in 13 of the 15 patients. One man had a marginal increase in tumour size, while in another it shrank (Johnston *et al.* 1984).

Surgical management of prolactinomas has resulted in ovulatory menstrual cycles in 40% of patients with macroadenomas and in 80% of patients with microadenomas (Hardy *et al.* 1978; Tucker *et al.* 1981; Richards *et al.* 1986). Operation does of course carry a risk of surgical complications, which necessarily includes hypopituitarism. In a review of the results of trans-sphenoidal surgery in eight series totalling 283 patients, the rate of cure, that is of persistent normalization of serum prolactin concentrations, ranged from 24 to 78% (Thorner *et al.* 1980). In general the larger the tumour, the smaller the chance of cure and bromocriptine is often needed postoperatively to normalize prolactin secretion and so induce ovulation. For instance, Thomson *et al.* (1985) reported that only 50% of patients with macroadenomas were satisfactorily treated surgically and none with a prolactin concentration of >10 000 mu/l was cured by the operation. Another problem associated with surgery is late recurrence of hyperprolactinaemia, which has been observed after initial postoperative normalization in 17–40% of patients with microadenomas (Rodman *et al.* 1984; Serri *et al.* 1983) and in up to 80% of patients with macroadenomas (Serri *et al.* 1983). When these results are considered, together with the efficacy of bromocriptine therapy in reducing the size of even large prolactinomas, the place of surgery becomes increasingly limited to patients in whom medical treatment has failed. Radiotherapy has been advocated in the management of large prolactinomas, both as primary treatment and as prophylaxis to avoid tumour enlargement during a subsequent pregnancy. It may be given as external beam (Grossman & Besser 1985) or as interstitial (Kelly *et al.* 1979) radiotherapy. We do not favour its use because the fall in serum prolactin concentrations following X-ray therapy is slow, hypopituitarism is a risk (Johnston *et al.* 1986) and our recent experience indicates that pituitary irradiation is an important cause of pituitary failure, with non-response to pulsatile LHRH therapy to induce ovulation (Armar *et al.* 1986).

The major controversy in the management of patients with prolactinomas, and the one that concerns gynaecologists most, is the choice of treatment for those who present with infertility. The main cause of concern for these patients is the known stimulatory effect of oestrogens on the growth of prolactinomas during pregnancy. In the case of microadenomas the risk is very small and in a recent review that summarized 16 series, totalling 246 patients with microadenomas who became pregnant, it was reported that only 1·6% had symptomatic enlargement of the tumour (Molitch 1985). In no case was surgical intervention necessary. We consider therefore that for patients with microadenomas it is inappropriate to advise any treatment other than medical suppression of hypersecretion of prolactin. In patients with macroprolactinomas, however, the risk that the lesion will expand during pregnancy has been reported to be as high as 37·5% (Gemzell & Wang 1979) and this apparently high risk has led some authorities to recommend pituitary destructive therapy before pregnancy. We think, however, that the risks of tumour enlargement have been overstated. In the frequently quoted review of Gemzell & Wang (1979) for instance, less than half the patients (21/56) with macroadenomas had, in fact, received treatment with bromocriptine for induction of ovulation. Indeed if we consider only the patients with macroadenomas who had received bromocriptine before pregnancy, the percentage of pregnancies in which tumour complications occurred was less than 20% (4/21) rather than the 37·5% usually quoted. However, it is also not known whether the macroadenomas had been shown to have regressed adequately on treatment with bromocriptine before conception, a practice that we consider very important (see below). Moreover, since the authors had not differentiated between micro- and macroadenomas in the group that had had pretreatment with surgery or radiotherapy, it is logical to assume that if only those with macroadenomas in this group of 67 patients were considered (Gemzell & Wang 1979, Table 5), the rate of tumour complications during pregnancy would almost certainly have been higher than the 7·1% quoted. Therefore, the protective value of prepregnancy destructive treatment of prolactin-secreting macroadenomas is by no means certain.

A similar analysis may be made of the results in a more recent review that summarized 11 series totalling 45 patients with macroadenomas, who became pregnant without having had prior treatment with surgery or radiotherapy (Molitch 1985). This review reported that of the women with macroadenomas 15·5% (7/45) had symptomatic and 8·9% (4/45) asymptomatic enlargement of the tumour during pregnancy. On the basis of this analysis it was concluded that the risk of clinically serious tumour enlargement during pregnancy was much higher in those patients with macroadenomas who had been treated with bromocriptine alone than in those who had treatment before pregnancy with surgery or radiotherapy. Before accepting this conclusion, however, careful analysis of the 11 series is required because two of the seven patients who had had symptomatic tumour enlargement had in fact been treated with human menopausal gonadotrophins and not bromocriptine (patient 1, Child *et al.* 1975; case 15, Bergh *et al.* 1978) and in the group of four patients who had asymptomatic tumour enlargement, one patient had

had a macroadenoma that was untreated before pregnancy (Crosignani *et al.* 1981, p. 709, line 15 right column) while in another (Randall *et al.* 1982, p. 21, last line right column), one cannot determine whether or not she had received bromocriptine before her pregnancy.

Finally for the other patients mentioned by Molitch (1985) there is no information in the original reports (cases 4 and 5, Bergh *et al.* 1978; subject C.O. with bitemporal hemianopsia at ninth month, Crosignani *et al.* 1981; patient 9, Lamberts *et al.* 1979; patient S.J. who actually had a micro- and not a macroadenoma as reported by Molitch Shewchuk *et al.* 1980; patient 2, Bergh *et al.* 1982, and Thorner *et al.* 1979, p. 773, line 14 left column) as to whether the macroprolactinoma had undergone regression on treatment with bromocriptine before the patients became pregnant. In fact, two of the patients (case 4, Bergh *et al.* 1978; and Thorner *et al.* 1979, p. 773) had conceived accidentally soon after the bromocriptine was started (at least case 4, Bergh *et al.* 1978).

Bergh *et al.* (1982) reported their experience of 19 pregnancies in 14 women with large prolactinomas who received bromocriptine as primary treatment. There was a serious complication in only one of the 19 pregnancies (development of a visual field defect at 30 weeks) and this was quickly reversed when bromocriptine was restarted. One possible reason for the rarity of the tumour expansion after adequate bromocriptine therapy is that the prolactinoma shrinks away from the walls of the expanded fossa and by the time the patient conceives, the enlarged fossa contains only a small tumour, so there is considerable room to accommodate any expansion that may occur. If ovulation is induced with drugs that are not dopaminergic agonists, such shrinkage does not occur and therefore room is not made for the pituitary expansion that occurs normally during pregnancy (Jacobs 1984).

Our policy is therefore to use bromocriptine as the primary therapy for prolactinomas regardless of tumour size. For patients with macroadenomas, we advise that pregnancy is deferred until a repeat CT scan has shown that the prolactinoma has shrunk at least to within the confines of the pituitary fossa. If the degree of shrinkage is inadequate, surgery is advised. It is a contentious point as to whether bromocriptine should be stopped once pregnancy is diagnosed. Although there has been no evidence of any hazard to the fetus in women given bromocriptine during pregnancy (Turkalj *et al.* 1982; Konopka *et al.* 1983) there is, nevertheless, evidence that bromocriptine does cross the term placenta (Bigazzi *et al.* 1979) and can reduce prolactin levels in the fetus (Maeda *et al.* 1983). On general principles therefore we advise stopping the bromocriptine once pregnancy is diagnosed.

We do not advise routine assessments of the visual fields during pregnancy, first because they encourage an inappropriate feeling of dread in the patient and second because when expansion does occur, it develops so rapidly that it would almost certainly be missed on such routine testing. Serial measurements of prolactin are also of disappointing value because it has been found that in patients with prolactinomas, maternal prolactin levels do not necessarily rise progressively during the pregnancy and the levels are not predictive of complications (Divers & Yen 1983). If pituitary expansion does occur and results in clinical symptoms (headache or impaired vision) we restart treatment with bromocriptine immediately. We have recently reported a 29-year-old patient who had presented with amenorrhoea and galactorrhoea caused by a large prolactinoma that had regressed only minimally on bromocriptine therapy when the patient conceived (Tan & Jacobs 1986). Treatment with bromocriptine was stopped when the pregnancy was diagnosed but 6 weeks later the prolactinoma had regrown, with suprasellar extension and compression of the cavernous sinus. When treatment with bromocriptine was started again, symptoms remitted within 24 h and serum prolactin concentrations fell dramatically from 54 000 u/l to 2800 u/l within 5 days and to 500 u/l 2 days after that. Pregnancy proceeded without complications and she gave birth to a healthy baby after spontaneous labour at term. One year after delivery, on treatment with bromocriptine, 5 mg daily, her serum prolactin concentration was within the normal range and the CT scan showed adequate shrinkage of the prolactinoma. Subsequently she has completed another pregnancy, during which she took bromocriptine throughout, and the pregnancy was free of any complications of prolactinoma.

In summary we consider that bromocriptine is the primary treatment of choice for prolactinomas of all sizes, irrespective of whether or not the patient desires fertility. We reserve surgery for patients in whom medical treatment has failed. If an operation is required the surgeon is encouraged to perform a selective adenectomy to retain anterior pituitary function, even at the risk of incomplete removal of the tumour. Long-term control can always be provided by post-operative treatment with bromocriptine.

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Phenytoin kinetics during pregnancy and the puerperium

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Summary. During pregnancy changes in maternal physiology and plasma composition may alter drug binding and dose requirements. We have measured plasma unbound and total phenytoin, and saliva concentrations at intervals in 11 pregnant epileptics. Plasma albumin concentrations were also measured in pregnant and non-pregnant women. Saliva phenytoin correlated closely with the plasma unbound concentrations ($r = 0{\cdot}98$). The saliva:plasma (S:P) ratio, reflecting the free fraction, was variable during pregnancy but tended to increase to maximal values at delivery and return to non-pregnant values within 2–8 weeks thereafter. Plasma albumin concentrations correlated poorly with phenytoin binding. Binding in umbilical cord plasma appeared higher than that in maternal plasma and total fetal concentrations correlated closely with maternal plasma concentrations at delivery. No ill effects of phenytoin were detected in the newborn infant. During the third trimester phenytoin dose increments were necessary to maintain therapeutic concentrations. After delivery maternal saliva phenytoin concentrations rose, and dose reductions were necessary to avoid clinical symptoms of toxicity. It is therefore appropriate to monitor saliva phenytoin concentrations regularly both during pregnancy and the puerperium.

Epilepsy afflicts an estimated 0·5% of the population (MacIntyre 1982), and 64% of the epileptics who attend this laboratory for monitoring of their drug medication receive phenytoin, which always requires careful dosage control.

During pregnancy changes in cardiovascular, gastrointestinal, hepatic and renal physiology (Eadie *et al.* 1977; Krauer *et al.* 1984) may substantially influence drug kinetics (Krauer *et al.* 1980). Reduced oral absorption of anticonvulsants has been reported (Ramsay *et al.* 1978) and a rise in progesterone has been implicated in inducing drug metabolism (Waddell & Butler 1957; Gabler & Hubbard 1972). Extracellular fluid volume increases and plasma composition changes (Gleichmann *et al.* 1973). Notably maternal total protein and albumin concentrations fall, particularly during the first trimester (Hytten & Leitch 1971), while free fatty acid concentrations rise (Burt 1960; Reboud *et al.* 1963). These factors result in reduced protein binding of highly bound drugs such as phenytoin (Dean *et al.* 1980; Ruprah *et al.* 1980; Chen *et al.* 1982; Perucca *et al.* 1981) and together with fetoplacental tissue growth they may contribute to a raised distribution volume and increased dose requirements during pregnancy (Lander *et al.* 1977).

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It is generally accepted that drug effect depends upon the free (unbound) concentration in the plasma (Leonard 1980). Thus in the presence of reduced or variable binding, total plasma concentration is not a valid monitor of drug effect.

To-date, with the exception of Chen *et al.* (1982), protein binding studies of phenytoin during pregnancy have been made only *in vitro*. In other conditions which disturb protein binding, saliva has been found to correlate closely with free phenytoin (Reynolds *et al.* 1976; Knott *et al.* 1982; Kilpatrick *et al.* 1984). In this study, plasma total, plasma free and saliva phenytoin concentrations have been measured at intervals during 11 pregnancies, in order to assess the changes in binding and free phenytoin with advancing gestation.

Subjects and methods

Eleven pregnant epileptic women were studied. All of them were receiving phenytoin and six had additional medication consisting of carbamazepine in two, valproate in two and phenobarbitone in two, one of these last two also received primidone and the other carbamazepine (Table 1); they were out-patients who attended the laboratory for sampling as part of their routine clinical care. They therefore entered our study at a somewhat random stage of pregnancy.

Saliva (0·5–1 ml) and plasma (2 ml heparinized blood) samples were taken simultaneously at intervals during pregnancy for drug analysis. Each patient also supplied one 26 ml blood sample for protein binding estimations as described previously (Knott *et al.* 1982). Protein binding was also measured in 16 non-pregnant women of child bearing age who were taking phenytoin without valproate. In six of the non-pregnant, and in six of the pregnant patients, plasma albumin concentrations were also measured.

In five patients, maternal and umbilical cord

Table 1. Clinical data of the patients in the study.

Patient	Age (years)	Parity	Drugs	Fit control*	Outcome	Apgar score at minute 1	5	10
1	23	Nulliparous	Phenytoin Valproate	Worse	M normal	8	10	9
2	22	Nulliparous	Phenytoin Valproate	Same	F normal	9	10	10
3	20	Nulliparous	Phenytoin	Same	F normal	—	9	10
4	33	Nulliparous	Phenytoin	Same	F normal	—	9	10
5	27	Nulliparous	Phenytoin	Same	M normal	—	9	10
6	23	Parous	Phenytoin	Same	M normal	9	10	10
7	27	Nulliparous	Phenytoin	Worse	F normal	—	9	10
8	21	Nulliparous	Phenytoin Carbamazepine	Worse; status epilepticus at term	M normal	8	9	10
9	33	Nulliparous	Phenytoin Carbamazepine	Better	F normal	8	9	10
10	27	Nulliparous	Phenytoin Phenobarbitone Primidone	Worse	F normal	9	10	10
11	33	Nulliparous	Phenytoin Phenobarbitone Carbamazepine	Same	M normal	9	10	10

* Compares fit control during pregnancy with the 6 months immediately before conception

Table 2. Phenytoin protein binding

Patients	n	Phenytoin protein binding (%)
Pregnancy		
early (10–24 weeks)	11	90·98 (3·08)
late (25–40 weeks)	11	87·55 (4·04)
At delivery		
Maternal	5	87·9 (5·3)
Cord	5	91·6 (2·6)
Non-pregnant	16	92·2 (1·5)

blood was taken at delivery for analysis of drug content and protein binding.

Drug concentrations were measured in saliva, plasma and ultrafiltrate using gas-liquid-chromatography with nitrogen detection as described previously (Knott *et al.* 1982). Intrinsic phenytoin clearance (clearance of the unbound fraction) was calculated using saliva concentrations as a predictor of the free fraction, from the equation:

$$\text{Intrinsic clearance (ml/min)} = \frac{\text{Dose } (\mu\text{g/min})}{\text{Saliva phenytoin concentration } (\mu\text{g/ml})}$$

Data are presented as mean and (SD) where appropriate, and differences have been analysed using Student's paired and unpaired t-tests.

Clinical data are given in Table 1. Most patients did not present to this laboratory until the second trimester. To examine the data, where appropriate pregnancy has been divided up into two periods: 'early pregnancy' (weeks 10–24) and 'late pregnancy' (weeks 25–40).

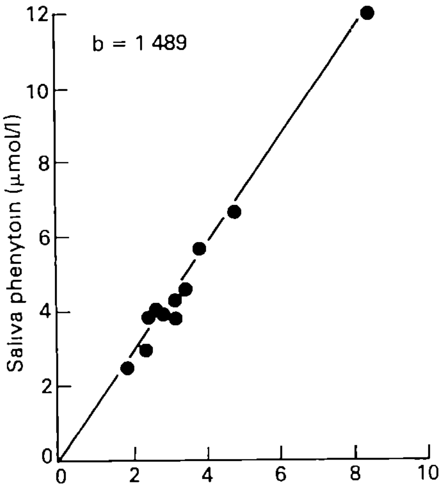

Fig. 1. Relation between saliva and plasma unbound phenytoin in all 11 pregnant patients taking phenytoin.

Results

Neonatal outcome

Babies in this study were all healthy and alert at birth (Table 1) with no overt signs of malformation.

Protein binding

During pregnancy the phenytoin free (unbound) fraction in the plasma varied from 7·3 to 18·5%. Mean figures for binding in early and late pregnancy, at delivery, in umbilical cord plasma and in non-pregnant women, are given in Table 2. Numbers were small and there was no significant difference between any of the groups.

The correlation between saliva phenytoin concentrations and plasma unbound phenytoin concentrations was highly significant ($r = 0{\cdot}983$; $P<0{\cdot}001$; Fig. 1). This allows the ratio of saliva and plasma phenytoin concentrations (S:P ratio) measured on the same occasion to be used as an index of the free fraction.

The mean albumin concentrations in the pregnant women, 37·7 (SD 3·3) mg/ml, did not differ significantly from those in the non-pregnant group of 41·2 (SD 5·2) ($0{\cdot}05<P<0{\cdot}2$). The correlation between albumin concentration and free phenytoin ($r = -0{\cdot}47$) was too weak to be of predictive value.

Phenytoin S:P ratios

S:P ratios measured during pregnancy and in the puerperium in the nine patients taking phenytoin without valproate are shown in Fig. 2. Because valproate is known to disturb phenytoin binding (Knott *et al.* 1982) results for two patients taking phenytoin with valproate are given in Fig. 3, together with saliva phenytoin and plasma valproate concentration. Samples were obtained from seven patients during early pregnancy when the mean S:P ratio was 0·118 (SD 0·018). The mean S:P ratio in late preg-

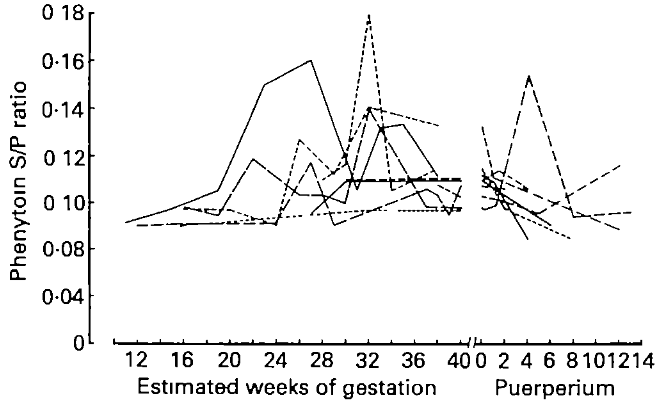

Fig. 2. Phenytoin saliva:plasma ratios during gestation and in the puerperium in nine epileptic women taking phenytoin without valproate. Samples could not be taken from one mother in the puerperium.

nancy for these patients was 0·163 (SD 0·036) and for all 11 patients 0·155 (SD 0·032). The rise in S:P ratio in pregnancy is significant ($P<0·001$) and is well exemplified in patients 1 and 2 (Fig. 3). S:P ratios returned to non-pregnant levels within 2–8 weeks of delivery. In patient 5 who refused a dose reduction in the early puerperium, phenytoin toxicity resulted and the S:P ratio rose.

Phenytoin clearance

Phenytoin doses and mean saliva concentrations are shown in Table 3. From these data the intrinsic clearance has been calculated, and the change in clearance with gestation and in the puerperium is presented in Fig. 4. Clearance appeared to fall between the first and second trimesters, to rise towards term, and decline rapidly in the puerperium. Dose increments were necessary to maintain saliva phenytoin concentrations within the therapeutic range as pregnancy progressed, while reductions were usually necessary in the puerperium to prevent phenytoin toxicity.

Placental transfer

Umbilical cord plasma concentrations of phenytoin at delivery correlated with maternal plasma

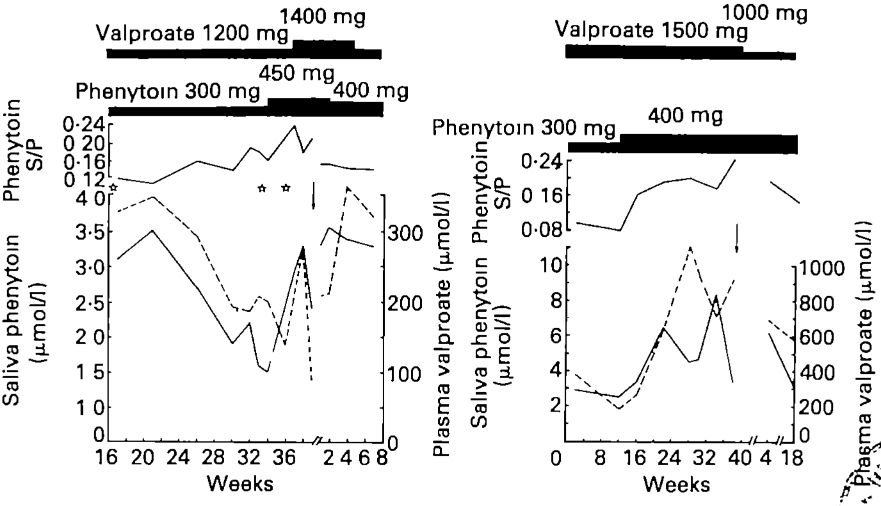

Fig. 3. Plasma valproate, saliva phenytoin (dotted line) and saliva/plasma phenytoin ratio in two pregnant epileptic women. ☆ indicates seizure, ↓ indicates delivery. Daily dosage of phenytoin and valproate shown above graphs.

Table 3. Phenytoin doses and saliva concentrations

Patient	Weeks of gestation	Dose (mg/day)	Saliva concentration (μmol/l) Mean (SD)	Number of samples
1	17–32	300	2·68 (0·65)	5
	33–39*	450	2·34 (0·79)	5
	39–3p	400	3·35 (0·05)	3
2	2–16	300	2·73 (1·01)	3
	22–38*	400	8·66 (1·90)	5
	2–4p	350	9·00 (0·85)	3
3	30–40*	450	3·50 (0·40)	4
	2p	450	4·3	1
4	27–40*	300	4·30 (0·30)	3
	6p	300	6·4	1
5	16–19	400	3·00 (0·85)	3
	22–32	500	7·12 (1·38)	4
	37–40*	550	8·00 (0·57)	3
	40–4p	550	11·00 (4·10)	3
	8–13p	450	12·30 (2·55)	3
6	38–40*	400	3·75 (0·64)	3
	1–8p	400	7·50 (4·06)	3
7	28–32	300	3·50 (1·59)	3
	34–40*	400	3·80 (0·28)	3
	8p	400	4·3	1
8	16	300	4·1	1
	20–24	325	5·15 (0·78)	3
	26–38*	350	3·23 (1·33)	3
	1–6p	350	7·83 (2·83)	4
9	12–40*	400	4·00 (0·48)	4
	1–3p	400	4·60 (0·10)	3
10	12–24	300	2·77 (0·74)	3
	27–31	350	3·93 (0·95)	3
	37–40*	450	6·88 (0·95)	4
	2p	450	6·0	1
11	11–15	100	0·30	2
	19	200	1·4	1
	23–38*	300	2·87 (1·22)	5
	1–4p	300	2·50 (1·27)	3

* Delivery, p weeks postpartum.

levels (*r*=0·994). Mean cord concentration, 21·98 (SD 13·37) μmol/l, was similar to the maternal plasma concentration, 21·85 (SD 14·7) μmol/l. Free concentrations in cord (1·66, SD 0·67 μmol/l) were lower than those in maternal plasma (2·26, SD 0·95 μmol/l). The mean fetal:maternal ratio for total drug was 1·07 (SD 0·12) and for free drug 0·75 (SD 0·17).

Discussion

From the variability of protein binding in pregnancy reported here, and by other workers (Dean *et al.* 1980; Ruprah *et al.* 1980; Chen *et al.* 1982; Perucca *et al.* 1981; Lander *et al.* 1977; Leonard 1980; Riva *et al.* 1984; Perucca & Crema 1982), it is clear that measuring total plasma phenytoin concentration during pregnancy is an inaccurate means of estimating all important free levels. Measuring free levels directly is invasive, time consuming and expensive.

Because anticonvulsant drugs are principally bound to albumin (Brodie 1965; Koch-Wesser & Sellers 1976; Monks *et al.* 1978), falling plasma albumin during pregnancy (Gleichmann *et al.* 1973; Riva *et al.* 1984) may be partly responsible for the reduced binding seen with highly bound drugs such as phenytoin (Dean *et al.* 1980; Chen *et al.* 1982; Leonard 1980; Riva *et al.* 1984;

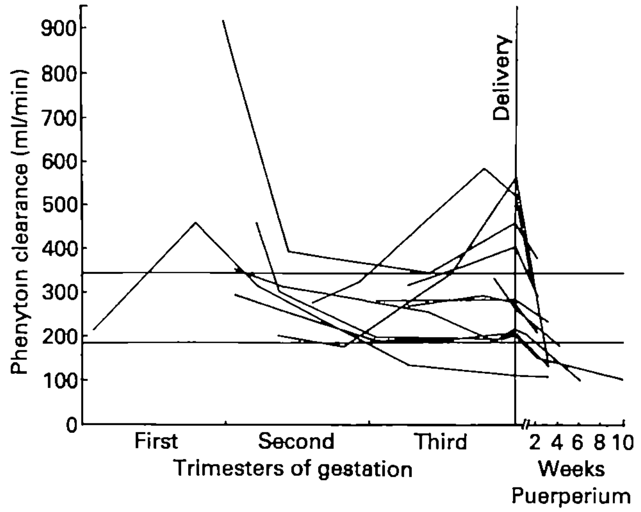

Fig. 4. Saliva phenytoin clearance during pregnancy and the puerperium in 11 epileptic women. Horizontal lines represent the normal range of phenytoin clearance (Knott 1985).

Perucca & Crema 1982). Good correlations between free phenytoin fraction and plasma albumin have been obtained when plasma spiked with phenytoin is diluted with buffer (Lunde *et al.* 1970), or in situations where hypoalbuminaemia is the sole factor affecting binding, such as occurs in the nephrotic syndrome (Gugler & Azarnoff 1976). Less good correlations have been obtained in conditions in which binding is disturbed by other factors, such as renal failure (Reidenberg 1981; Levy *et al.* 1976). The use of albumin concentrations to predict drug binding during pregnancy (Perucca & Crema 1982) has been suggested, but additional factors frequently contribute to the reduction in phenytoin binding (Knott *et al.* 1982; Koch-Wesser & Sellers 1976; Hooper *et al.* 1974; Perucca & Richens, 1979; Perucca 1980; Stock *et al.* 1980) and such prediction is clearly invalidated by the present study. However, saliva phenytoin bears the same close relation to free phenytoin in pregnant patients as it does in the non-pregnant epileptic population and when protein binding is depressed whether by renal failure (Reynolds *et al.* 1976) or by concurrent valproate administration (Knott *et al.* 1982). The S:P ratio is therefore a useful measure of the free phenytoin fraction in these as in other individuals, and the same saliva phenytoin therapeutic range of 4–9 µmol/l may be employed (Knott & Reynolds 1984). In addition it is simpler, cheaper and less invasive than plasma free drug measurement.

The present work therefore confirms that phenytoin protein binding falls in pregnancy, and shows wide inter- and intra-individual variation. This phenomenon has been shown to occur with valproate co-medication (Knott *et al.* 1982), but was apparent here also in the nine individuals who were not taking valproate.

Phenytoin doses during pregnancy and in the puerperium

The claim that phenytoin dose increments are often necessary to maintain therapeutic concentrations in compliant pregnant epileptics (Eadie *et al.* 1977; Lander *et al.* 1977; Mygind *et al.* 1976; Dam *et al.* 1979; Landon & Kirkley 1979) is supported here. This was found particularly during the third trimester when, in the absence of dose increments, saliva and plasma phenytoin concentrations fell, apparent clearance values reaching a maximum at delivery and thereafter falling. Phenytoin clearance may *appear* to be high in the first trimester, but this may be a result of vomiting or poor compliance for fear of teratogenesis in early pregnancy because during the second trimester, after compliance was strongly urged and with no change in dose, saliva phenytoin clearance appeared to decrease.

Dam *et al.* (1979) found that plasma clearance of phenytoin fluctuated considerably during pregnancy, and tended to increase to a maximum just before delivery, as did intrinsic clearance in the present study. Eadie et al. (1977) suggested that increased phenytoin clearance may result partly from enhanced rate of biotransformation and that the balance between oestrogen and progesterone concentrations may contribute to such changes in clearance during pregnancy. The aetiology is probably multifactorial including (i) increased metabolic capacity, (ii) raised extracellular fluid volume, (iii) variations in drug absorption, particularly as antacids which reduce phenytoin bioavailability (Carter *et al.* 1981) are commonly used, and (iv) some variability may occur as a result of altering concentrations of enzyme inducing co-medicants. For example, in the present study, two patients (10 and 11) received phenytoin with phenobarbitone and a reduction in saliva phenobarbitone concentration was associated with increased saliva phenytoin concentration in the absence of a dose change.

Phenytoin placental transfer

Phenytoin, a weak acid with a pK_a value of 8·3, would be very slightly more ionized in maternal than fetal plasma. A free fetal:maternal ratio, calculated from the Henderson–Hasselbalch equation, and assuming a pH gradient across the placenta of 0·1, would be predicted to be 0·98 at equilibrium. The total phenytoin fetal:maternal ratio, calculated from known protein binding in fetal and maternal blood, would be 1·47. Cord:maternal plasma concentration ratios measured here were somewhat lower, possibly because at delivery the pH gradient was greater than 0·1, or because of fluctuations in maternal levels and consequent incomplete equilibration. Total phenytoin concentrations were found to be approximately equal in maternal and fetal plasma in this study as in others (Mirkin 1971; Sherwin *et al.* 1974; Baughman & Randinitis 1970; Landon & Kirkley 1979).

The 'therapeutic' concentrations of phenytoin found in these babies were not associated with any evidence of neonatal depression, nor indeed was there evidence of teratogenesis in any baby (admittedly a small series). Some deliveries took place beyond our reach, but those mothers that were followed up were encouraged to breast feed to mitigate possible withdrawal fits. None occurred, and neonatal saliva phenytoin fell rapidly in the first 2 weeks, and remained negligible despite appreciable quantities of phenytoin in mothers' milk (unpublished observation).

Phenytoin remains the most widely prescribed anticonvulsant, so that many epileptics become pregnant while receiving it. It is not a powerful teratogen, and undesirable effects in mother and baby can be minimized by careful dosage control. We therefore urge that saliva phenytoin be monitored regularly during pregnancy and in the puerperium in order to make appropriate dose adjustments.

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Blood group antibody screening tests during pregnancy

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Summary. In a 2-year period 667 sera from approximately 70 000 (0·95%) antenatal patients were found to contain 726 atypical red blood cell antibodies. Overall, 66% of the immunized mothers were rhesus (D) positive. Apart from four antibody specificities to rhesus system antigens, knowledge of the rhesus (D) group gave no guide to the ability of the patients to form any of the remaining 21 specificities encountered. Of the 726 antibodies 221 (30%) were not detected in the initial sample tested and 50 of the 92 patients who produced antibodies during pregnancy had not developed detectable antibody when they were sampled at 28 weeks. The significance of these late onset antibodies is discussed both in relation to the risk of haemolytic disease in the newborn and transfusion reactions in the mother. An optimum protocol for testing is defined which takes account of antibody production during the pregnancy and use of this protocol constitutes an attempt to combine maximum clinical safety with minimal consumption of resources.

Haemolytic disease of the newborn (HDN) is classically associated with maternal alloimmunization to the rhesus (D) factor, less often with antibodies such as anti-c, anti-E and anti-K. Except for rare anecdotal cases, most other red cell antibodies encountered in pregnancy are of little danger to the fetus. But virtually all maternal antibodies can present problems for the woman since they can cause haemolytic transfusion reactions. Because of the frequent need to provide blood around the time of delivery, everyone involved should appreciate the potential hazards for the sensitized patient. It is essential to anticipate difficulties relating to the supply of compatible blood since extensively grouped blood is not regularly available.

All antenatal patients should, therefore, have blood samples assessed for evidence of alloimmunization. But there is no uniform agreement about the need for, and the timing of, repeat antibody screening tests during pregnancy. We have reviewed 2 years' serological data, in an attempt to determine the optimal time(s) for taking samples which would combine maximal safety for mother and baby with economy of resources and effort.

Patients and methods

In the 2 years 1983 and 1984, there were approximately 70 000 births in the region served by the Oxford Regional Blood Transfusion Centre (RTC). Blood samples from all pregnant women were screened for atypical red cell antibodies. Approximately half the blood samples were tested at the RTC, the remainder at six district hospital blood bank laboratories.

Sampling protocols and test procedures varied between laboratories, but were essentially similar to those used at the RTC as follows. All patients were tested at the booking visit and again at about 34–36 weeks gestation. Patients with a history of previous blood transfusion, and

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all rhesus (D) negative patients, were checked again at about 28 weeks. For the purpose of this study the booking sample was defined as the first sample received before the 26th week. Antibody screening procedures, biased towards the detection of high thermal optimum antibodies, included a pre-enzyme modified cell method (three separate cells), and the low ionic strength saline antiglobulin method (two cells). All sera found to give positive screening results were tested more extensively at the RTC for confirmation of antibody identity and potency; more frequent blood samples were obtained from these patients for the remainder of the pregnancy.

Alloimmunized patients with potent antibodies, and with consorts positive for the corresponding blood group antigens, were delivered at the direction of local obstetricians and at a time determined by a combination of one or more of the following factors: maternal serum antibody potency; amniotic fluid ΔOD^{453} and lecithin/sphingomyelin ratio results; previous history of HDN.

Cord blood specimens were initially tested at hospital laboratories for haemoglobin, bilirubin, blood group and direct antiglobulin tests. Many were also later tested at the RTC for genotype and eluate studies. Neonatal treatment was instigated at the direction of local paediatricians. Details of immediate neonatal treatment were obtained by a simple questionnaire issued by the RTC. Information about subsequent therapy, however, was rarely available.

Details of maternal transfusion history, parity and gestation were culled from answers to routine questions posed on antenatal serology request cards.

Results

Of the 70 000 women tested 667 (0·95%) produced a total of 726 high thermal optimum, atypical red cell antibodies. The nature and frequency of the antibodies encountered is shown in Table 1. Of the 726 antibodies identified 394 (54%) were to antigens within the rhesus blood group system. Because of the relatively greater clinical significance of these antibodies they are shown in more detail than the remainder, which are simply collated into blood group systems. A total of 31 patients produced antibodies to antigens in two different blood group systems; one to three systems and one to antigens in four different systems. Overall 441 (66%) of the antibody producers were rhesus (D) positive. After omitting those patients producing anti-D, anti-c, anti-f and anti-e, the proportion that was rhesus (D) positive was 382 of 451 (85%).

Of the 726 antibodies identified 221 (30%) were not detected in the first sample tested during the pregnancy. Of 92 patients producing antibodies during pregnancy 50 did not have detectable antibody in the first sample tested or in the 28th week sample.

Table 1 also shows the overall proportion of sensitized patients known to have had a previous blood transfusion (29%). Of the 405 patients who had detectable antibody in the initial sample of the pregnancy 163 (40%) were known to have been transfused previously; where antibodies were not found until later in pregnancy the proportion was 21% (38 of 184). In the general antenatal population, the frequency of a known history of previous transfusion was 4·7% (228 of 4832).

During the 2-year period, 31 babies showed evidence of severe haemolysis caused by atypical red cell antibodies (see Table 2). There were 20 exchange transfusions and 11 fetal losses comprising seven second trimester losses, two perinatal deaths, and two therapeutic terminations for very poor prognosis. All 11 deaths were attributable to maternal anti-D sensitization and occurred in the early detection group. The frequency of exchange transfusion amongst incompatible offspring in the 'early' anti-D group was 21% (12 of 58) and 8% (5 of 59) in the 'later' group. Whereas 3 of 17 (18%) incompatible babies required exchange transfusion in the 'early' anti-c group, there were no exchanges in the 'later' anti-c group. The mean cord blood haemogloblin values of the infants requiring exchange transfusion were: 11·1 g/dl (7·7–17·1) in the 'early' anti-D group, 13·5 g/dl (11·4–17·7) in the 'late' anti-D group and 17·0 g/dl (13·7–22·9) in the 'early' anti-c group.

The other 13 fetal losses shown in Table 2 were not deemed to be attributable to HDN because either the antibody potency was too low and/or the period of fetal contact with the antibody was too short. Post-mortem studies, where performed, excluded HDN as the cause of fetal death. Four sensitized patients moved from the Oxford region during the pregnancy and the outcome could not be determined.

Table 1. Antibody detection rate in first blood specimen tested during pregnancy, and the association of history of blood transfusion with antibody production

Antibody specificity	No. of examples	Results of antibody tests on first blood sample			Previous history of blood transfusion		
		Detected	Not detected	Not known*	Yes	No	Not known
Anti-D; D+C D+E	158	90	61 (39%)	7	32 (20%)	98	28
Anti-c	49	24	22 (45%)	3	22 (45%)	21	6
Anti-C; Ce; e; f	19	9	10 (53%)	0	8 (42%)	8	3
Anti-E	130	90	34 (26%)	6	38 (29%)	73	19
Anti-C^w	38	33	2 (5%)	3	4 (11%)	30	4
Anti-M; N	11	4	7 (64%)	0	0	10	1
Anti-S, s	13	9	4 (31%)	0	7 (54%)	4	2
Anti-Lu^a; Lu^b	3	2	1 (33%)	0	0	3	0
Anti-K; k; Kp^a; Kp^b; Wk^a	76	63	11 (14%)	2	63 (83%)	9	4
Anti-Le^a, Le^b; Le^{a+b}	182	109	50 (27%)	23	16 (9%)	139	27
Anti-Fy^a; Fy^b	26	22	4 (15%)	0	18 (69%)	4	4
Anti-Jk^a; Jk^b	21	5	15 (71%)	1	2 (10%)	17	2
Total	726	459 (63%)	221 (30%)	46 (6%)	210 (29%)	416 (57%)	100 (14%)

*Results of tests performed before 26 weeks gestation were not known. first test thereafter showed presence of antibody.

Table 2. Comparison of outcome of pregnancy in 'early' and 'late' antibody-detection groups

Antibody specificity and time of detection	Outcome of pregnancy and neonatal treatment						
	HDN-associated fetal losses	Exchange transfusion	Phototherapy	No treatment	Not known	Infant known to be negative for antigen	Other fetal losses
Anti-D							
First sample ($n = 90$)	11	12*	9	26	2	20	10†
Later ($n = 61$)	0	5	14	40	1	1	0
Anti-c							
First sample ($n = 24$)	0	3	4	11	1	3	2‡
Later ($n = 22$)	0	0	3	18	0	0	1§

* Includes two women treated with plasma exchange and one intrauterine transfusion.

† Five miscarriages; three therapeutic terminations and two intrauterine deaths (not HDN).

‡ One miscarriage; 1 termination (not HDN).

§ One stillbirth (not HDN).

Discussion

With the increasing need for efficient and economic testing, this study set out to see what changes, if any, should be made to current protocols. In particular the value of repeat serological tests was examined. Although there has been no previous specific study on this matter, many have opted for at least two serological tests during pregnancy on all women (Beal 1979; Austin *et al.* 1976; Editorial 1981).

Blood grouping and red cell antibody testing, though heavily biased towards the prevention and management of the continuing problems of HDN, also give advanced warning of possible difficulties about blood supply (Biale & Dvilansky 1982). This latter point is especially relevant to the urgency of blood demands late in pregnancy, and the fact that 16–22% of women (at least in this area) have blood cross-matched during pregnancy.

The majority of the 667 sensitized women were at risk of a haemolytic reaction if transfused, and blood supplies could have been delayed without early warning of the presence of atypical antibodies. Indeed, many smaller hospital blood banks could not provide suitable blood immediately for these patients from their relatively small blood stocks. Also, neither flying squad nor other emergency blood stocks would have been tested for many of the blood groups for which corresponding antibodies were found. It is therefore essential for the safe management of the mother to foresee any difficulties with the supply of blood. Antibody screening protocols must reflect this problem and RTC's and blood banks should coordinate their services accordingly.

Knowledge of the rhesus (D) group of antenatal patients is essential for the proper provision of anti-rhesus (D) prophylaxis. Given the opportunities for blood grouping, sample-labelling and reporting errors, it is important that the blood group is checked on more than one occasion. Since the blood group of the vast majority of the women in their first pregnancy (who constitute 40–45% of the pregnant population) will not be known, these women in particular should have their blood grouped during the first trimester when abortion is most likely and on at least one other occasion later in the pregnancy. The blood group of a significant proportion of multiparae will also not be known and would thus qualify for the same sampling protocol.

In this study at least 30% of women who developed blood group antibodies did so after the first assay had been performed. Certain antibodies were produced more often during the pregnancy (Jk^a/Jk^b, M/N) than others (C^w, Kell etc.), possibly because of the relatively high incidence in the general population and thus the consorts, of the corresponding antigens. It is apparent that rhesus (D) positive as well as rhesus (D) negative patients can readily form atypical antibodies, since in this survey, 66% of those producing antibodies were rhesus (D) positive. Furthermore, after excluding those patients with anti-D, and anti-c/anti-e/anti-f, which can only be made by rhesus (D) negative and rhesus (D) positive patients respectively, the rhesus (D) type of the remainder precisely matches the distribution of the rhesus (D) type (85% positive) in the antenatal population. Thus, knowledge of the rhesus (D) type gives no indication of the ability to form antibodies, and therefore all patients should be retested on a second occasion in pregnancy. This permits not only blood group confirmation, but also a later check for recently developed or previously missed antibodies.

In spite of prophylaxis, HDN has far from disappeared. Although clinical problems caused by antibodies other than anti-D have proportionately increased during the past 15 years (Hardy & Napier 1981), those caused by anti-D are still both more severe and more frequent. The fetal mortality and morbidity shown in Table 2 illustrate the continuing problems, with 11 of 120 (9·2%) fetal losses and 17 of 120 (14·2%) exchange transfusions in known rhesus (D) incompatible offspring of sensitized mothers. Also although there were no fetal losses and fewer exchange transfusions in the 'late' antibody-detection group, 5 of 60 (8·3%) as against 12 of 60 (20%), even these babies are not totally safe. Since the extent of treatment an infant receives is not only a feature of the maternal antibody potency, but also reflects the period of contact of that antibody with the fetal cells, early delivery of the affected fetus is often necessary. Thus it follows that it is essential to have as much warning of potential difficulties as is possible. We therefore recommend that all rhesus (D) negative patients should have additional serological tests at 28 weeks, although others advocate even more frequent sampling

(Queenan 1982; Whitfield 1984). We believe that 28 weeks is early enough to give adequate warning because there were no fetal losses due to HDN in the 'late' antibody-detection group either in this study or during the previous 15 years in which this policy has been advocated and full records maintained. The quality of the antibody screen on the initial sample is, however, vital: poor antibody detection methods may miss weak antibodies, which by 28 weeks might have reached dangerous or even lethal levels.

Next in importance to anti-D comes anti-c which caused three babies to require exchange transfusion during this study. Again, infants of mothers with antibodies at booking were more likely to require exchange transfusion 3 of 19 (15·8%) than those where the antibodies were found later (no exchanges). However, none of the three babies were born dangerously anaemic and all babies in this study affected by anti-c required treatment only for hyperbilirubinaemia, although anecdotal cases of severely anaemic infants have been reported elsewhere. A further illustration of the comparative importance of anti-c and anti-D is that whereas the proportion of the antenatal population eligible to make either antibody is very similar (17% and 15%), the number of patients who developed antibody was 49 (1 in 243) and 258 (1 in 66) respectively. Of the women who were sensitized to c 45% were known to have been transfused. It has been previously suggested that all women of child-bearing age should be both c grouped and given c negative blood when appropriate (Fraser & Tovey 1976). Such a policy would have prevented fewer than half the sensitizations seen and only a very few fetal problems, yet have required both considerable time and effort.

Of the sensitized women 29% were known to have been transfused previously: this is a much higher proportion than that found overall in the pregnant population (4·7%). However, transfusion is not always the stimulus for the antibody production. Thus, although 20% of patients with anti-D were known to have been transfused previously, none had been given rhesus (D) incompatible blood and in most of them it is likely that the obstetric incident necessitating a transfusion was responsible for the sensitization. Conversely as with anti-K production, blood transfusion is usually the cause of sensitization. Overall, previously transfused women are at a relatively high risk of producing atypical antibodies, since 40% of those with antibodies at booking and 21% of those developing antibodies later in the pregnancy were known to have been transfused previously. Because of this higher risk, and because of the difficulties of supplying some of the rarer types of compatible blood we recommend that all previously transfused patients be checked for the second time, like rhesus (D) negative women, at 28 weeks gestation. In spite of this, of 92 patients producing antibody during pregnancy, 50 (54%) were known not to have had detectable antibody even by 28 weeks. A third sample is clearly required from these high-risk groups at a time when the incidence of feto-maternal haemorrhage is approaching maximum (Cohen *et al.* 1964). A sample at 34–36 weeks gestation would appear to be satisfactory and permit not only early delivery of the at-risk child, but also allow reasonable warning for appropriate provision of compatible blood.

None of the remaining antibodies listed in Table 1 caused overt clinical problems to the infant. The only other examples of HDN reported to us were caused by anti-A/B antibodies, for which we and many others do not regularly screen. However, not only are these regular rather than atypical antibodies, but also given the high frequency of ABO incompatibility during pregnancy (approximately 25%), they cause very few and usually only minor problems. Although none of the other antibodies listed in Table 1 caused major problems for the infants, it is prudent for these sensitized mothers to be delivered at hospitals with the necessary facilities for the adequate care of the mother at delivery and for the infant after birth.

Our blood sampling recommendation in pregnancy has been vindicated by the absence of unexpected fetal losses and with very few reported cross-match difficulties. It is as follows: the first specimen taken in early pregnancy should ideally coincide with rubella and initial haematological testing to reduce the number of venepunctures performed; women who are either rhesus (D) negative or who have been previously transfused should be rechecked at 28 weeks gestation, and all women regardless of rhesus (D) type or transfusion history should be tested again at about 34–36 weeks. Sampling protocols are adjusted for those women found to have antibodies and reflect both the antibody specificity and potency, and the corresponding blood type of the consort.

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The significance of anti-c alloimmunization in pregnancy

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Summary. In an 8-year period, 177 of 280 000 pregnancies were complicated by maternal anti-c alloimmunization. Although there was one neonatal death associated with anti-c haemolytic disease of the newborn, only two infants were severely anaemic at birth. A total of 11 babies required exchange transfusion, but nine of these developed hyperbilirubinaemia alone. The remaining c positive infants were either unaffected or only mildly affected by erythroblastosis fetalis. A strategy for management of these pregnancies is outlined, and proposed methods of prevention and serological control are discussed.

Haemolytic disease of the newborn (HDN) is classically associated with maternal alloimmunization to the rhesus (D) factor, less often with antibodies such as anti-c, anti-E and anti-Kell. Most other atypical red cell antibodies encountered in pregnancy are generally of little consequence to the fetus.

Experience at the Oxford Regional Blood Transfusion Centre (RTC) suggests that, apart from anti-D, anti-c causes most clinical problems (Bowell *et al.* 1986). We have therefore analysed our records of relevant pregnancies presenting during an 8-year period to determine both the frequency of anti-c sensitization, and the incidence and nature of resulting clinical difficulties. The value of both existing and proposed methods of serological control (Phillips 1986), together with the likely benefits of a possible method of reducing antisensitization (Fraser & Tovey 1976), have also been examined.

Patients and methods

In the Oxford Region there are approximately 35 000 pregnancies annually. All antenatal patients, regardless both of rhesus (D) status and parity, have at least two red cell serology investigations during pregnancy. Approximately half these tests are carried out at the Oxford RTC and the remainder at six district general hospital laboratories. Antibody screening methods, although showing minor differences between laboratories, are essentially similar, comprising both two-stage enzyme and indirect antiglobulin (IAGT) methods. Individual samples from between two and five control-cell donors are used for antibody screening purposes.

All samples giving positive screening tests were further tested at the RTC to confirm both the identity and titre of the antibody. When more than one antibody specificity was found in any sample, the anti-c potency was determined using control cells which were heterozygous for c and negative for the other antigen(s). Repeat antibody investigations and titrations were performed monthly until 28 weeks gestation, and thereafter fortnightly until delivery. Paternal rhesus genotypes were determined at the RTC.

Details regarding the patient's transfusion history were obtained from the request card accompanying each sample. After delivery a

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detailed questionnaire was sent to either the local obstetrician or haematologist to determine both the laboratory data and clinical details for each patient. Case notes were examined when necessary to obtain information not available from the questionnaires and request cards.

Decisions regarding the obstetric management and timing of delivery were taken by local obstetricians at the 12 district hospitals, with advice from the RTC when requested or deemed necessary. Management of the infant during the neonatal period was under the direction of the local paediatric staff.

This study covers the 8-year period 1978–1985 and 280 000 pregnancies.

Results

Of the 280 000 pregnancies 177 showed evidence of anti-c alloimmunization, these were derived from 162 patients, with 15 having two pregnancies during the eight year period. In 82 patients the sera contained additional atypical red cell antibodies: 67 contained anti-E and 19 had one or more of the following: anti-C^w, Le^a, Le^b, Jk^a, Jk^b, s, Kell, Kp^a.

Examination of transfusion histories showed that 83 (51%) patients had been previously transfused, 68 (42%) had not, and the transfusion history of 11 (7%) patients could not be determined.

Maximum antibody titration values ranged from neat to 1/256 (IAGT): in 129 pregnancies the maximum anti-c potency was 1/8 or less by IAGT, the values in 45 others are shown in Table 1 and the remaining three had titres of 1/16 and 1/64 (c negative infants), and 1/64 (non-HDN intrauterine death).

The outcomes of the 177 pregnancies included two spontaneous abortions, two intrauterine deaths (non-HDN), one induced abortion (high maternal AFP) 169 singleton infants and three sets of twins.

There was one neonatal death (case CB178) during the first year of the study. This infant weighed 2·73 kg and was in extremely poor condition at birth, very difficult to resuscitate with the stigmata of severe erythroblastosis (cord blood haemoglobin 8·1 g/dl, ascites and hepatosplenomegaly). Although an immediate exchange transfusion successfully raised the haemoglobin level from 5·5 to 11·1 g/dl, the infant continued to show very poor respiratory effort, had persistent acidosis, and had obvious neurological (CNS) damage. It would appear that the CNS damage, which was thought to have occurred antenatally, influenced the continuing haematological management in that no further exchange transfusions were attempted. The infant died on the seventh day. At post-mortem, in addition to the obvious indications of severe HDN, the brain was found to be completely infarcted and semi-liquified.

A total of 13 babies required exchange transfusion (Table 1) but two of these were deemed not to have been for anti-c HDN (one had severe bruising following facial presentation, maternal anti-c titre 1/8 and cord blood Hb 22·9 g/dl; the other was both E and c positive but the maternal serum contained anti-E 1/32 and anti-c neat only, cord blood haemoglobin 20·1 g/dl). Of the remaining 11 infants (Table 2) two were born with severe anaemia, haemoglobin values 8·1 (case CB178) and 9·1 g/dl, at 37 and 38 weeks of gestation respectively; both mothers had a history of previous HDN (exchange transfusion and self-resolving hyperbilirubinaemia respectively) and had anti-c alone. Nine babies required exchange transfusion because of neonatal hyperbilirubinaemia, one was born at 36 weeks, two at 37 weeks, two at 38 weeks and four at 39 weeks gestation. In seven of these nine pregnancies anti-c was found either alone or was the only antibody present which was incompatible with the infant's red cells; two mothers had additional incompatible antibodies (one had

Table 1. Relation between maternal anti-c potency and requirement for exchange transfusion in 45 pregnancies

		Maximum maternal anti-c titre				
Neonatal exchange transfusion	*n*	1/16	1/32	1/64	1/128	1/256
Yes	11	1	3	4	1	2*
No	33	10	12	7	3	1
Not known	1	0	0	1†	0	0

* One neonatal death

† Delivered abroad and outcome unknown

Table 2. Relation between maternal anti-c potency and cord blood haemoglobin values in 45 pregnancies

		Maximum maternal anti-c titre				
Cord blood haemoglobin value (g/dl)	*n*	1/16	1/32	1/64	1/128	1/256
<10	2	0	0	1	0	1*
10–14	9	1	3	3	1	1
>14	19	4	8	5	1	1
Not known†	15	6	4	3‡	2	0

* Neonatal death.

† None of these infants required exchange transfusion (see note ‡)

‡ One patient delivered abroad and outcome unknown.

anti-c and anti-E of equivalent titre, 1/16; the other had very weak anti-Jk^a). Three infants received two exchange transfusions, the remainder only one.

Six women had an amniocentesis in the second or third trimester, in two no clear fluid could be obtained, three of the others had a single amniocentesis and one had five. The three patients having a single amniocentesis had ΔOD^{453} values equivalent to Liley's lowest zone: although two of the three resulting infants required an exchange transfusion none was anaemic. Patient CB178 had an anterior placenta and had five attempts at amniocentesis between 26 and 30 weeks gestation; only one, at 27 weeks, successfully obtained clear fluid giving a ΔOD^{453} value in the upper half of Liley's mid-zone. This patient declined further offers of amniocentesis after the 30th week.

Discussion

Anti-c is but one of many atypical antibodies that can be produced by rhesus (D) positive patients during pregnancy. This antibody has been reported to cause both HDN and haemolytic transfusion reactions (Astrup & Kornstad 1977; Mollison 1983). Although in our experience (Bowell *et al.* 1986) other antibodies such as anti-E and anti-Kell are found more frequently in pregnancy, the importance of anti-c sensitization assumes greater significance because the incidence of the c positive group in the general (and therefore the paternal) population is relatively high at 84%.

Although 177 of 280 000 (0·63 per 1000) pregnancies showed evidence of anti-c alloimmunization during the 8-year period, it is unlikely that any single hospital in the Oxford Region would have experienced more than two or three such pregnancies annually. Thus any individual obstetrician will have rarely encountered patients with this type of sensitization, and may well be unfamiliar with both its significance and method of management. The aims of this report are to highlight both the specific and relative importance of anti-c antibodies found during pregnancy.

Maternal anti-c alloimmunization appears to be a rare cause of fetal death, since during the 8 years of the study there was only one neonatal death associated with anti-c HDN; it is also not clear whether the CNS damage in this infant resulted from HDN or from some other underlying pathology. Furthermore, it is possible that the erythroblastosis might have been reduced if there had been ultrasound guidance for the amniocenteses and greater compliance from the patient, thus resulting in earlier delivery. Infant morbidity caused by anti-c also appears to be usually minor and infrequent, with only two babies being born severely anaemic and only 11 receiving exchange transfusion (4/100 000 births). Comparable figures for rhesus (D) HDN during the same period were 30 deaths, 49 severely anaemic infants and 131 receiving exchange transfusion (47/100 000 births).

A further indication of the relative immunogenicity of the rhesus D and c antigens can be obtained by contrasting the sensitization rates for both antibodies. Approximately 16% of the patients studied would have been c negative, i.e. 44 800. Of this number, 177 (0·39%) developed anti-c antibodies: this contrasts with an anti-D sensitization rate of 1·7% for rhesus (D) negative patients (Bowell *et al.* 1985). Additionally, the incidence of anti-D sensitization is artificially lowered probably by a factor of four by post-delivery prophylaxis, and unlike anti-c very few examples of anti-D are produced following transfusion.

Of the 162 c sensitized patients 82 (51%) had at least one other blood group antibody. The strong association with anti-E sensitization, 67 of 162 (41%), should serve as a reminder of the need to ensure that patients with pre-existing anti-E are transfused with c negative blood when appropriate. It is also important to check that patients with anti-c do not have additional allo-antibodies, for although these might not compound any HDN, they would most certainly delay the provision of compatible blood for transfusion.

A particular transfusion problem for c sensitized obstetric patients is to ensure that rhesus (D) negative blood, which has a double dose of c antigen, is not used as an emergency measure during major haemorrhagic episodes. Some clinical staff see rhesus (D) negative blood as the universal donor type, suitable for all patients; transfusion of such blood to these patients would probably not only cause serious transfusion reactions, but also add to the danger of erythroblastosis in subsequent pregnancies.

Although amniocentesis was successful in only four patients, it is reassuring to note that the amniotic fluid ΔOD^{453} values gave some indication of the degree of HDN. Unfortunately the one pregnancy (CB178) where essential information might have been provided by amniocentesis was complicated both by an anterior placenta and a lack of ultrasound scanning facility for amniocentesis. However, the single ΔOD^{453} value obtained at 27 weeks in this pregnancy gave the highest reading in the study, in the upper half of Liley's mid zone. Although one can only speculate what might have happened during the remainder of this pregnancy, it is our belief that amniocentesis does have a role to play in the management of c sensitized pregnancies. Ideally the threshold at which this procedure is applied should be a little lower than that at which severe in-utero problems might occur. Our threshold, therefore, has been set at a titre of 1/32 IAGT, one titration point down from that at which severe anaemia was first seen but at a level where 20% of infants received exchange transfusion for severe hyperbilirubinaemia (Tables 1 and 2). Since even the most severely affected babies in this study were not born until or after 36 weeks gestation, it is only in a very exceptional case that an amniocentesis would be necessary before 28 weeks. Probably for most, a single amniocentesis at 34 weeks would be adequate: this would allow either a projection of a date for safe delivery or indicate that the pregnancy should proceed to term.

Although just over half the women in the study were known to have been transfused previously, in many instances it was not known whether a feto-maternal bleed or transfusion caused the immunization. Only five of the 11 women whose infants required exchange transfusion, and one of the two with severely anaemic infants, had been previously transfused. Thus a policy of c grouping all women who have blood transfusions before the menopause and transfusing them with c negative blood when appropriate (Fraser & Tovey 1976) would have prevented very few clinical problems during the study period and yet have involved considerable effort and expense. We believe, therefore, that such a policy is not justifiable.

Given the relatively infrequent and usually minor problems associated with c sensitized pregnancies, it would seem that a prophylactic regimen akin to that currently used to prevent rhesus (D) HDN is unnecessary.

An unexpected problem found during the study was the frequent omission of the necessary cord blood tests at delivery, especially when the maternal anti-c level was 1/8 or below. On 20 occasions no cord blood samples were collected at delivery, and on a further eight, blood group and direct antiglobulin tests were not performed; cord blood haemoglobin and bilirubin levels were also not determined on 45 and 52 occasions respectively. Although we have encountered relatively few clinical problems due to anti-c sensitization, failure to test cord blood samples could cause early laboratory indications of erythroblastosis to be missed, with consequent risks to the infants. There was one such case during this study, when mother and infant were discharged before test results were known, and the baby had to be readmitted for exchange transfusion after severe jaundice had developed.

It has recently been suggested that an automated assay of anti-c potency (Phillips 1986), as now widely used for anti-D throughout the United Kingdom (Urbaniak 1985), could lead to a better prediction of clinical outcome. Whilst this assumption is probably correct, it would seem an impractible suggestion for most laboratories since even we, testing samples from a relatively large antenatal population, would expect to see no more than two or three c sensitized patients monthly. The only conceivable manner in which both the time and expense could be justified would be if the automated quantitation method was performed at either national or super-regional laboratories. The benefits of such a system, however, would be lost if any resulting communication difficulties prevented rapid return of data to enable adequate clinical control.

Although we have seen two instances of severe anaemia with one neonatal death, and we are aware of other anecdotal reports of severe problems (Hardy & Napier 1981), it appears that close serological control with regular manual antibody potency estimates, coupled with amniocentesis when necessary, is adequate for the safe management of all but the rarest examples of maternal alloimmunization. Pregnancies where the maternal anti-c titre remains at or below 1/16 should be allowed to proceed to term. Delivery for the remainder is generally not necessary before the 36th week and should be planned in accordance with the interpretation of amniotic fluid ΔOD^{453} values.

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Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants

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Summary. An examination of the maternal vascular response to placentation shows that physiological changes in the placental bed normally extend from the decidua into the inner myometrium. In pre-eclampsia and in a proportion of pregnancies with small-for-gestational age infants (SGA) the physiological changes are restricted to the decidual segments alone. In addition, complete absence of physiological changes throughout the entire length of some spiral arteries is seen in pre-eclampsia and SGA. This new observation is confirmed in a study of basal plates of placentas from abnormal pregnancies. Intraluminal endovascular trophoblast may be seen in the placental bed spiral arteries in the third trimester in pre-eclampsia and SGA, a feature not seen beyond the second trimester in normal pregnancy. These findings point to a defect in the normal interaction between migratory trophoblast and maternal uterine tissues in pre-eclampsia and in SGA.

The human placenta receives its blood supply from more than 100 uteroplacental arteries (Brosens & Dixon 1966; Boyd & Hamilton 1970) which are elaborated by the action of migratory interstitial and endovascular trophoblast on the spiral arteries in the placental bed (Harris & Ramsey 1966; Brosens *et al.* 1967; Boyd & Hamilton 1970). The conversion of the spiral arteries of the non-pregnant uterus to the uteroplacental arteries has been termed 'physiological changes' (Brosens *et al.* 1967) and, in normal pregnancy, these trophoblast-induced vascular adaptations extend back from their openings into the intervillous space to where the spiral arteries originate from their parent radial arteries in the inner myometrium. It is thought that this vascular phenomenon is effected in two stages, the conversion of the decidual segments of the spiral arteries by a wave of endovascular trophoblast migration in the first trimester and the myometrial segments by a subsequent wave in the second trimester (Robertson *et al.* 1975; Pijnenborg *et al.* 1983).

There is good evidence from haemodynamic studies (Browne & Veall 1953; Dixon *et al.* 1963; Lunell *et al.* 1979, 1982; Clavero-Nunez 1980; Campbell *et al.* 1983; Trudinger *et al.* 1985; Pearce *et al.* 1986) that the blood supply to the fetoplacental unit is impaired in pre-eclampsia and in most pregnancies with small-for-gestational age infants (SGA) even when they are not associated with the hypertensive disorders of pregnancy. A plausible morphological explanation for the reduced placental blood supply in these pregnancy disorders was the discovery (Brosens *et al.* 1972) that in pre-eclampsia and in a proportion of pregnancies

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with SGA the physiological vascular changes are restricted to the decidual segments of the uteroplacental arteries leaving the myometrial segments unaltered in their musculoelastic architecture and thereby undisturbed and responsive to vasomotor influences. It was subsequently postulated (Robertson *et al.* 1975) that this defective maternal vascular response to placentation is due to inhibition of the second wave of endovascular trophoblast migration that normally occurs from about 16 weeks gestation onwards. Although there are differences of opinion on aspects of interpretation of morphological features, other investigators (Sheppard & Bonnar 1976; Brosens *et al.* 1977; Gerretsen *et al.* 1981; Hustin *et al.* 1983; Pearce *et al.* 1986) agree that, in pre-eclampsia and in some pregnancies with SGA, the maternal vascular response to placentation is something less than adequate.

On the other hand, restriction to physiological vascular changes cannot be the only factor contributing to a reduction in placental blood supply as not all pre-eclamptic pregnancies with incompletely formed uteroplacental arteries are complicated by SGA and a substantial proportion of those with SGA unassociated with pre-eclampsia apparently have fully developed physiological vascular changes (Sheppard & Bonnar 1976; Brosens *et al.* 1977; Gerretsen *et al.* 1981; Hustin *et al.* 1983). Another possible factor, which has never been investigated, although suggested (Robertson *et al.* 1985), is that in pre-eclampsia and in SGA there may be significantly fewer than the normal number of uteroplacental arteries formed. This idea was reinforced by the finding in a recent instance of SGA (Pearce *et al.* 1986) that a placental bed biopsy contained a fully developed uteroplacental artery extending from the myometrium to the intervillous space and a second spiral artery showing no evidence of physiological changes throughout its course. It was therefore decided to review all our archived material of placental bed biopsies and caesarean hysterectomy specimens in an attempt to assess the proportion of spiral arteries in the placental bed converted to uteroplacental arteries and the proportion uninvolved with physiological changes throughout their whole course from myometrium through the decidua. The material came from pregnancies complicated by hypertensive disorders with or without SGA, pregnancies with idiopathic SGA and from pregnancies with none of these disorders. To supplement this review of placental bed vascular anatomy, a study was made also of the basal plate, containing the terminations of the uteroplacental arteries, in a series of delivered placentas. This series included placentas from normal and abnormal pregnancies.

Materials and methods

Placental bed tissue

Two caesarean hysterectomy specimens from pre-eclamptic pregnancies and five caesarean hysterectomy specimens from normal pregnancies with infants of normal birthweights were obtained as described previously (Brosens *et al.* 1967; Robertson *et al.* 1967). Placental bed biopsies were obtained at caesarean section from normal and abnormal pregnancies at St George's Hospital, London, King's College Hospital, London and St Rafael-Gasthuisberg Hospital, Leuven. A total of 94 biopsies, histologically ascertained to be from the central zone of the placental bed and containing spiral arteries for morphological assessment, were studied.

Placental bed biopsies were processed by methods described by Brosens *et al.* (1967). Sections were cut from each block for haematoxylin and eosin (HE) staining, supplemented by sections stained by periodic-acid-Schiff (PAS), trichrome and elastica techniques when thought necessary to provide more detailed information.

Placentas

Placentas from normal and abnormal pregnancies derived from vaginal deliveries and at caesarean section were examined. Not all placentas were from cases in which the placental bed was also available for assessment of the uteroplacental vasculature. A total of 69 placentas was studied, 17 from normal pregnancies, 48 from abnormal pregnancies and four that were subsequently excluded because the available clinical data were inadequate.

The placentas were fixed in formal-saline for 5–7 days after which the entire placenta was cut into vertical strips, each about 1 cm in width. The following blocks were taken (modified from Fox 1978): (i) random blocks from the basal plate along every second slice from the central area of the placenta, (ii) two sections from the edge of the placenta, to include the basal plate, randomly taken but at opposite edges to each other.

The blocks were processed routinely and sections stained with HE and other supplementary stains as performed with the placental bed biopsies.

The maternal uteroplacental vasculature in both the placental bed and the basal plate was assessed in ignorance of the clinical details of the pregnancy.

Clinical criteria

For this study normal pregnancies were defined as those which were not complicated by pre-eclampsia, essential hypertension, SGA, diabetes mellitus or a combination of these disorders. Placental bed biopsies and placentas obtained at caesarean section performed for reasons such as cephalopelvic disproportion, breech presentation, unstable fetal lie, rhesus isoimmunization, failure to progress during labour and for previous caesarean section, and placentas obtained from vaginal deliveries following spontaneous normal labour comprised the normal material.

Clinical criteria for pre-eclampsia were a minimum blood pressure reading of 140/90 mmHg twice ≥4h apart associated with proteinuria of ≥500mg/l. If pre-existing hypertension was present at the outset of pregnancy, then a rise of 20 mmHg diastolic pressure with proteinuria was accepted as superimposition of pre-eclampsia on essential hypertension. Pre-existing hypertension, whether of the essential or renal type, was diagnosed when the blood pressure reading exceeded 120/80 mmHg in the non-pregnant state or during the first half of pregnancy. Terminal hypertension was the occurrence of hypertension near or at term but unassociated with proteinuria. SGA was defined as a birthweight below the 10th centile for gestational age according to Thomson *et al.* (1968) for the babies born in London and according to Lubchenco *et al.* (1963) for those born in Leuven. Because much of this study was retrospective, using archived material, the distinction between SGA and actual intrauterine fetal growth retardation had not been made in most cases. All such cases were therefore classified as the former with an unknown proportion of the latter included. There were three patients with diabetes mellitus dependent on insulin therapy but none with gestational diabetes.

Results

Placental bed tissue

From each of the five caesarean hysterectomy specimens from 'normal' pregnancies there were sufficient serial sections available to enable studies of the individual arteries in their course through myometrium and decidua from their origin from the radial arteries. From this, it was possible to determine that each radial artery terminates as two or three spiral arteries.

The physiological vascular changes seen in normal pregnancies were those described in other studies (Harris & Ramsey 1966; Brosens *et al.* 1967; Sheppard & Bonnar 1974) and will not be detailed further. In summary, spiral arteries in the placental bed lose their muscular and elastic components which are replaced by a fibrinoid layer of variable thickness in which trophoblastic cells are embedded (Fig. 1). These uteroplacental arteries are sinusoidally distended, extending from their origin in the myometrium through the decidua into the intervillous space (Fig. 2).

A review of sections from the two caesarean hysterectomy specimens derived from pregnancies complicated by pre-eclampsia confirmed previous observations (Brosens *et al.* 1972; Sheppard & Bonnar 1976; Gerretsen *et al.* 1981; Hustin *et al.* 1983) that the physiological vascular changes do not extend from the decidual to the myometrial segments of the spiral arteries (Fig. 3). Additionally, three in eight decidual segments had not undergone physiological changes but had retained the morphology of arteries in the non-pregnant uterus (Fig. 4). This observation was confirmed in the study of the placental bed biopsies in that some biopsies showed decidual spiral arteries with physiological changes whereas other biopsies showed decidual spiral arteries unaltered in their morphology (Table 1).

In all pre-eclamptic pregnancies whether or not complicated by SGA and/or essential hypertension, the *myometrial* segments of spiral arteries showed no evidence of trophoblast-induced physiological changes. On the other hand, absence of physiological changes in myometrial segments was observed in two-thirds

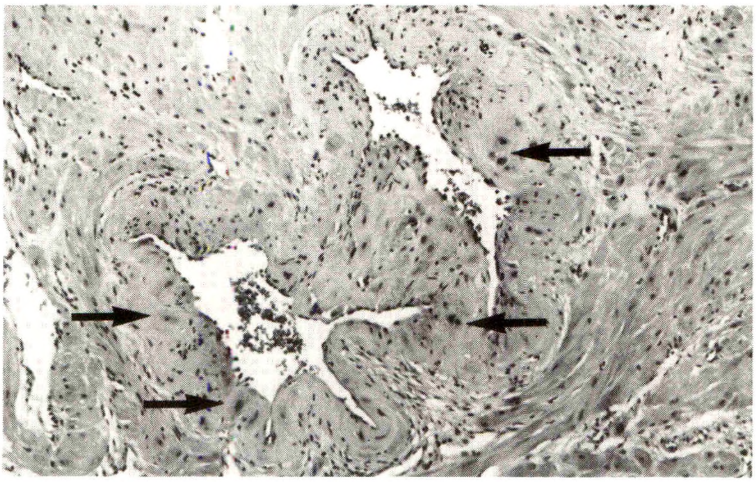

Fig. 1. Normal pregnancy at 36 weeks gestation: physiological changes in a myometrial segment of spiral artery. The arterial wall has been replaced by fibrinoid in which trophoblast is embedded (arrows). Haematoxylin and eosin × 75.

(16/24) of spiral arteries in patients with SGA infants alone.

Total absence of physiological vascular changes in some *decidual* segments was noted also in pregnancies complicated by pre-eclampsia or SGA or both, regardless of the presence or absence of essential hypertension. About half of the sampled arteries derived from abnormal pregnancies showed that they had not been affected by endovascular trophoblast, remaining in the same state as spiral arteries in the non-pregnant uterus (Fig. 5).

Placental basal plate

From the 69 placentas studied, maternal vessels were seen in the sections taken from 54 specimens but insufficient clinical data were available for four of them. This left 50 placentas for which assessment of the maternal uteroplacental vasculature in the basal plate could be correlated with clinical condition and outcome. Uteroplacental arteries, that is spiral arteries showing physiological vascular changes, were detected in 44 (Fig. 6); 15 were from normal pregnancies

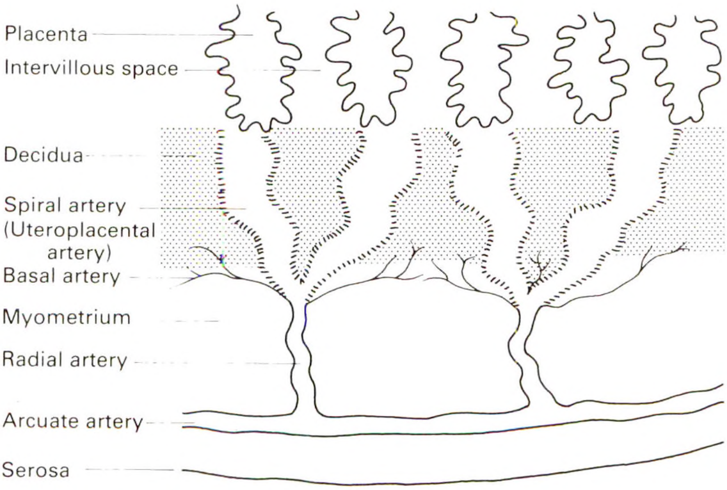

Fig. 2. Diagram of normal blood supply to the placenta. Note the termination of radial arteries each into two spiral arteries which have been physiologically converted (hatched). For clarity the marked coiling and distension have not been drawn.

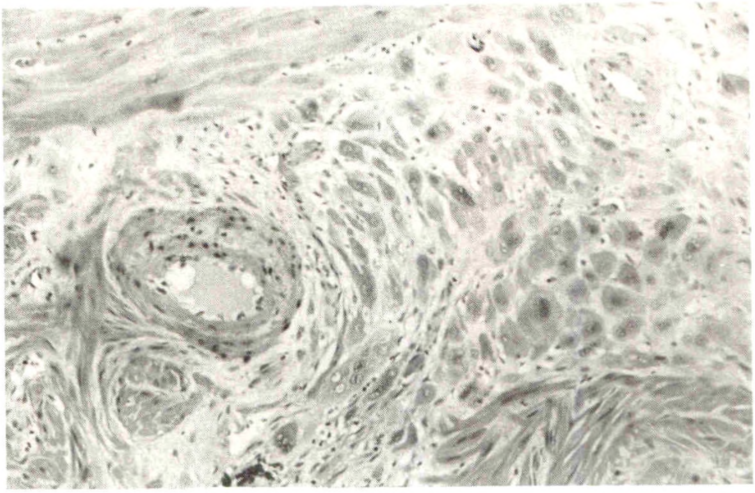

Fig. 3. Pre-eclamptic pregnancy at 34 weeks gestation: myometrial segments of spiral artery show absence of physiological changes. Note the infiltration of the surrounding interstitium by migratory trophoblast confirming placental bed. Haematoxylin and eosin × 112.

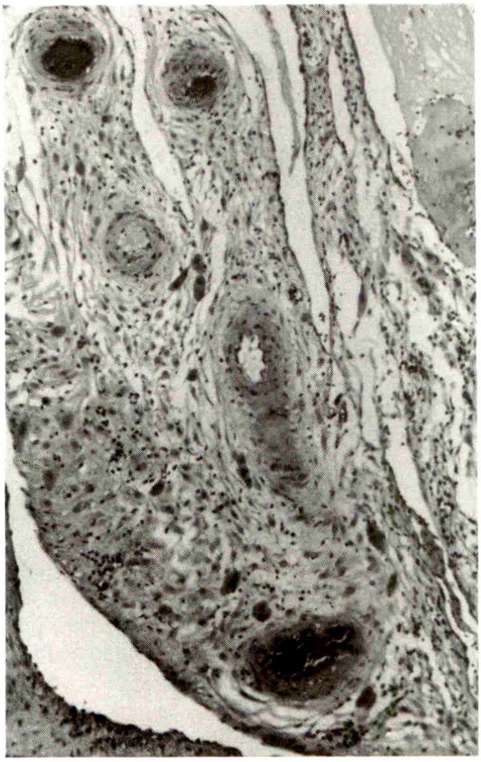

Fig. 4. Pre-eclampsia with small-for-gestational age (SGA) at 31 weeks gestation: decidual segments of spiral artery show absence of physiological changes despite the presence of plentiful nonvillous migratory trophoblast in the decidua. Haematoxylin and eosin × 68.

(100%) and 29 were from abnormal pregnancies (83%). Spiral arteries unaffected by physiological changes were seen in 20 placentas (Fig. 7), all of which were from abnormal pregnancies. In 14 of these 20 placentas from abnormal pregnancies both uteroplacental and unaltered spiral arteries were observed in different sections of the basal plate; thus, six had only spiral arteries not showing physiological changes (Table 2).

It should be noted that blocks taken from the edge of the placenta contained maternal arteries for study in only 12 cases. Both uteroplacental arteries and unconverted spiral arteries were seen in these marginal blocks from normal and abnormal pregnancies.

Luminal endovascular trophoblast

In the course of these studies endovascular trophoblast was noted in eight cases either free in the lumen or more often attached to the intima and all eight cases were from abnormal pregnancies, which were of 28–38 weeks gestation (Fig. 8). This feature was not seen in the uteroplacental arteries in normal pregnancies.

Discussion

There is general agreement on the anatomy of the blood supply to the human non-pregnant uterus (Dalgaard 1946; Lundgren 1957; Harris & Ramsey 1966; Boyd & Hamilton 1970). The

Table 1. Vascular changes in placental bed biopsies

Pregnancy complications	*n*	Decidual segments: Phys changes	Decidual segments: No phys changes	Decidual segments: Partial changes*	Myometrial segments: Phys changes	Myometrial segments: No phys changes	Myometrial segments: Partial changes
None (normal)	18	18	0	0	18	0	0
Hypertensive disorders							
Without SGA	14‡	4	8	2	0	11	0
With SGA	32†	13	15	3	0	31	1
SGA without hypertension	24	14	8	2	5	16	3
Diabetes mellitus (uncomplicated)	2	2	0	0	2	0	0
Terminal hypertension	4	4	0	0	3	1	0

* 'Partial changes' include those where there was a mixture of arteries with and without physiological changes and also arteries showing only part of their circumference affected by physiological changes.

† One biopsy contained no decidual segment; ‡ three biopsies contained no myometrial segment.

Phys, physiological; SGA, small-for-gestational age.

arcuate arteries derive from the uterine arteries and run in the outer third of the myometrium, giving off two sets of vessels, the centrifugal ones which nourish the outer one-third of the myometrium and the centripetal ones which branch in a fan-like manner towards the endometrium. These centripetally directed arteries are the radial arteries and they give off basal branches that supply only the basal endometrium and then break up into terminal spiral arteries. These terminal spiral arteries course through the endometrium giving off numerous vessels that pass laterally to supply the neighbouring stroma and glands. The spiral arteries terminate in the outer third of the endometrium as a leash of arterioles.

There is disagreement about the pattern of branching as the radial artery terminates. Dalgaard (1946) thought that division of the radial artery into two or more arteries did not occur and that a spiral artery was merely a continuation of the radial artery. Harris & Ramsey (1966) subscribe to this view as their writing

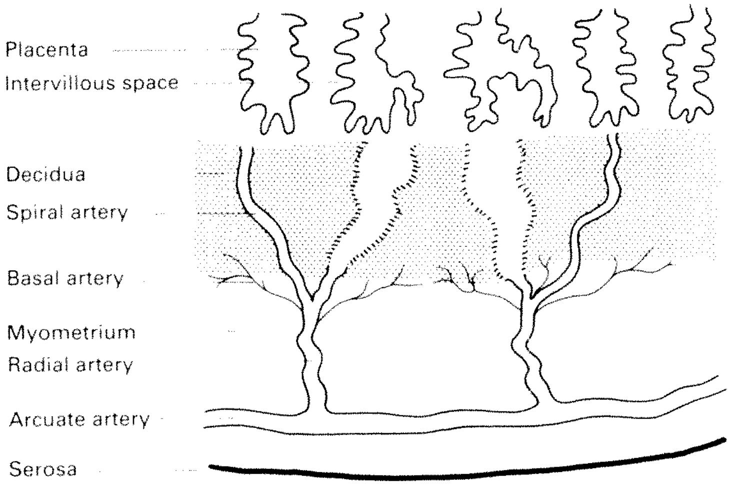

Fig. 5. Diagram of abnormal blood supply to the placenta. Note physiological changes (hatched) in some decidual segments of spiral arteries but absent in others. Myometrial segments are drawn without physiological changes, as in pre-eclampsia, but these segments may show physiological changes in some cases of SGA.

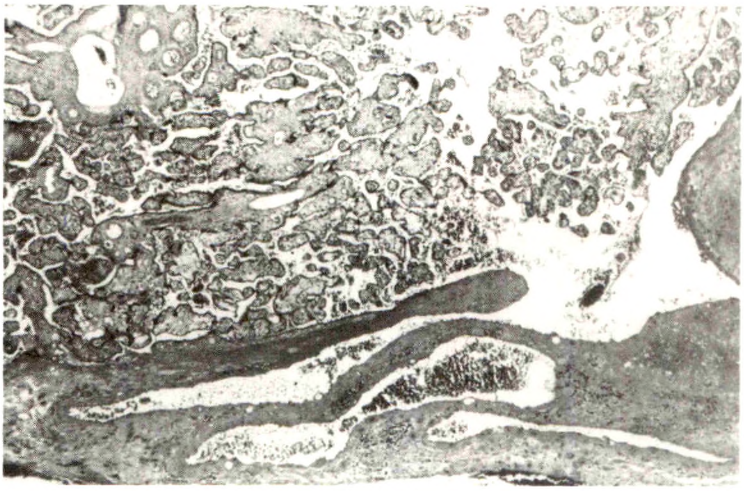

Fig. 6. Normal pregnancy at 37 weeks gestation: several cuts across a coiled uteroplacental artery in the basal plate where it opens into the intervillous space. Haematoxylin and eosin × 30.

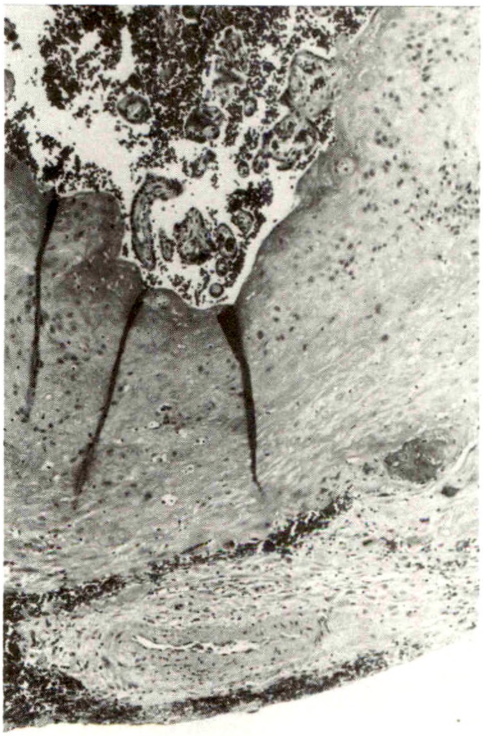

Fig. 7. Pre-eclampsia with SGA at 34 weeks gestation: spiral artery in the basal plate without physiological changes and retaining its musculoelastic structure. Haematoxylin and eosin × 67.

suggests that the radial arteries are called 'spiral' arteries only upon entering the endometrium. Brosens *et al.* (1967) considered that each radial artery divides into two or more spiral arteries. Our study confirms this latter view. The fact that one radial artery terminates as two or three spiral arteries is important as it explains the not infrequent finding that a uteroplacental artery and an adjacent artery without physiological changes may be seen apparently emanating from a single radial artery in a placental bed biopsy.

Our observations on the histology of physiological changes in the spiral arteries of the placental bed in normal pregnancy do not differ from those of others (Brosens *et al.* 1967, 1977; Sheppard & Bonnar 1974; Gerretsen *et al.* 1981; Hustin *et al.* 1983) and further discussion is unnecessary.

Previous workers (Brosens *et al.* 1972, 1977; Robertson *et al.* 1975; Sheppard & Bonnar 1976; Gerretsen *et al.* 1981; Hustin *et al.* 1983) have found that in pregnancies complicated by pre-eclampsia and/or SGA, the extent of these changes is confined generally to the decidual segments; in other words, physiological changes are not observed in the myometrial segments of the spiral arteries. Our study confirms this observation and, in addition, has shown that some spiral arteries remain unconverted to uteroplacental arteries throughout their entire length. The latter finding has been reported previously in three out of four patients from whom placental bed biopsies yielded decidual segments of spiral arteries (De Wolf *et al.* 1980). In the pres-

Table 2. Placental basal plate: maternal vascular pathology

	Pregnancy		
	Normal (n = 15)	Abnormal (n = 35)	Total (n = 50)
Physiological vascular changes alone	15	15	30
Physiological vascular changes and unconverted spiral arteries	0	14	14
Unconverted spiral arteries alone	0	6	6

ent study, we found as many as half of the abnormal pregnancies showed this absence of physiological changes throughout the entire length of some spiral arteries clearly indicating that they had not been colonized by trophoblast at any stage of gestation.

This new observation of total absence of physiological changes in a proportion of spiral arteries added to the earlier finding of restriction of physiological changes to the decidual segments of the spiral arteries has important implications. The first is that the maternal vascular response to placentation in abnormal pregnancies may be inadequate both qualitatively, as shown by the restriction of physiological changes, as well as quantitatively, as shown by the reduction in the number of uteroplacental arteries actually formed.

It was considered unwise to apply statistical analysis to our results because of the formidable sampling factors inherent in studies of placental bed biopsies and of random blocks of delivered placentas. Nonetheless, it would appear that in normal human pregnancy virtually every spiral artery in the path of migratory trophoblast is subject to physiological changes in the establishment of haemochorial placentation whereas in pre-eclampsia and in SGA many spiral arteries are missed or partially resist involvement with migratory trophoblast. Insofar as the placental bed biopsies are concerned, it must be pointed out also that these came from pregnancies with severe pre-eclampsia and SGA. With the modern approach to treatment, milder cases of these conditions are not subjected to caesarean section and hence biopsies are not performed. To counterbalance this selection factor the findings in the basal plate of delivered placentas give strong support to the above thesis.

It is tempting to suggest that a reduced number of uteroplacental arteries and a restriction of physiological changes to the decidual seg-

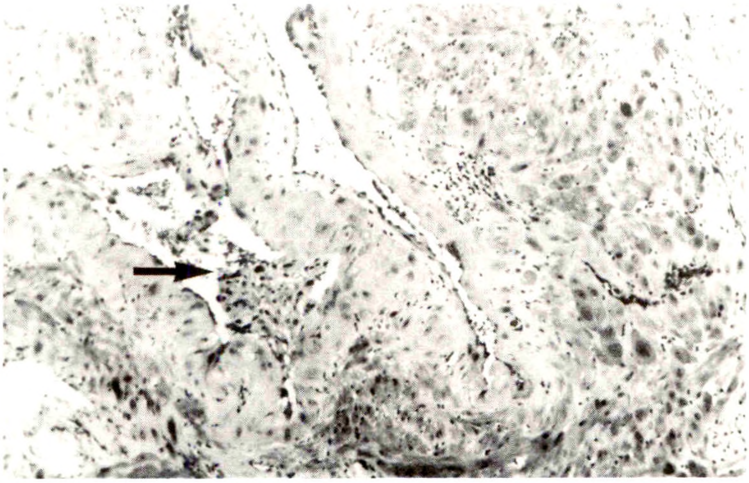

Fig. 8. Pre-eclampsia with SGA at 32 weeks gestation: endovascular trophoblast is seen in the lumen (arrow) of a spiral (uteroplacental) artery at the junction of the decidua (top) with the myometrium (bottom). The segment of this artery deeper in the myometrium showed no physiological changes. Haematoxylin and eosin × 105.

ments of those that are formed is an adequate explanation for SGA, whether or not it occurs in association with maternal hypertension. Our results do not substantiate this postulate as there were pre-eclamptic pregnancies without SGA yet with uteroplacental vasculature as defective as those additionally complicated by SGA. It may be that the apparent paradox could be explained by concentrating attention on fetal growth retardation as opposed to SGA. True fetal growth retardation can occur *in utero* yet such infants, when born, may be above the 10th centile (Keirse 1981). On the other hand, many SGA infants will have shown no evidence of growth retardation on monitoring *in utero*. It will require a prospective correlative study to determine whether or not a morphologically defective uteroplacental vasculature is constant in growth retardation, as it is in pre-eclampsia but not in SGA. Nor can our results support an inadequate vascular response to placentation as the cause of pre-eclampsia since a similar defect may be seen in some pregnancies with SGA but without pre-eclampsia. What can be suggested with confidence is that the two conditions are characterized by a defective interaction of migratory trophoblast with uterine tissues in the establishment and proper development of haemochorial placentation. It is perfectly possible that different aetiological factors can act to produce the same morphological pattern of defective placentation and, while the hypertensive disorders of pregnancy and SGA frequently coexist, it does not necessarily mean that they share aetiological factors.

The finding of intraluminal cytotrophoblast in the uteroplacental arteries in the third trimester in pregnancies with SGA and pre-eclampsia, a phenomenon not encountered in normal pregnancies, is further evidence of defective interaction between fetal and maternal tissue. This could be due to increased resistance on the part of maternal tissue or to decreased aggressiveness of the trophoblast or to a combination of both. The fact that the intraluminal trophoblast was found in abnormal pregnancies at between 28 and 38 weeks gestation, whereas all the 'normal' pregnancies were closer to term, may be considered to weaken the significance of this finding. But there have been sufficient investigations of the placental bed at or near term in normal pregnancies and there are enough of our normal preterm pregnancies to convince us that intraluminal trophoblast must be a rare finding in the third trimester of normal pregnancy (Brosens *et al.* 1967).

Since the uteroplacental arteries open into the intervillous space, the maternal vascular response to pregnancy may be studied also from the basal plate of the delivered placenta. This is advantageous when placental bed biopsies are not performed, as in vaginal deliveries, and in centres where the placental bed biopsy technique is not practised, or where it is contraindicated as in excessive maternal bleeding. However, the finding of characteristic uteroplacental arteries in the basal plate may not be reliable as an indication of normality since the myometrial segments of these vessels may be devoid of physiological changes. This caveat is reinforced by our study of the basal plate where uteroplacental arteries were observed in both normal and abnormal pregnancies, and also where uteroplacental and unconverted spiral arteries were both seen in some abnormal pregnancies. What may prove to be more useful diagnostically is the finding of spiral arteries without physiological changes. These were seen in 57% of placentas derived from abnormal pregnancies but none was observed in placentas from normal pregnancies.

Althabe *et al.* (1985) studied placental basal plates of normal and SGA infants and found absence of trophoblastic migration in arteries in basal plates of SGA infants but they were uncertain if these were basal or spiral arteries. They also found lack of physiological vascular changes in arteries of the basal decidua obtained by curettage of the placental bed but their published illustration does not show any interstitial trophoblast indicating either marginal or non-placental bed tissue. Furthermore, the arteries illustrated are of such small calibre that they are almost certainly basal arteries which are not involved in physiological changes (Brosens *et al.* 1967).

It is known that maternal vascular changes in the peripheral zones of the placental bed may be incomplete because of the centrifugal diminishing of non-villous trophoblast migration towards the periphery of the placental bed (Pijnenborg *et al.* 1981). Our finding of unaltered decidual segments of spiral arteries in blocks from the margin of the placenta in two normal pregnancies in the present study reflects this feature of migratory trophoblast and further emphasizes the pitfalls of studying maternal vascular changes in biopsies from the margin of the placental bed.

From this and other studies it would now seem to be beyond dispute that in the hypertensive disorders of pregnancy, particularly in pre-eclampsia, and in some cases of SGA whether associated with maternal hypertension or not, there is a significant defect in the maternal vascular response to placentation. Moreover, the finding of intraluminal endovascular trophoblast in the lumens of placental bed spiral arteries in the third trimester in cases of pre-eclampsia and SGA, when this feature is not seen beyond the second trimester in normal pregnancies, clearly points to a more general defect in the normal interaction between migratory trophoblast and maternal uterine tissues.

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The relation between the need for intubation at birth, abnormal cardiotocograms in labour and cord artery blood gas and pH values

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Summary. A consecutive series of 56 infants of 32 weeks gestation or more who were resuscitated at birth by endotracheal intubation was studied to determine the occurrence of abnormal cardiotocograph traces and acidosis as determined by cord artery blood measurements. Thirty-two infants (57%) had neither cardiotocographic abnormalities nor acidosis; in this group the factors associated with the need for intubation were meconium stained amniotic fluid, operative delivery, anaesthetic agents given to the mother, a tight nuchal cord, and traumatic vaginal delivery. The need for intubation at birth should not automatically be regarded as evidence of intrapartum hypoxia or disturbed acid-base balance.

Failure to establish spontaneous ventilation at birth is traditionally termed 'asphyxia neonatorum' (Donald 1959). Originally many causes of asphyxia neonatorum were recognized, including immaturity, meconium inhalation, pneumothorax, cerebral trauma, haemorrhage, congenital malformation, and infection (Capon 1959). This definition of asphyxia does not distinguish between babies who are born hypoxic and babies who are born normally oxygenated and become hypoxic subsequently due to failure to establish ventilation.

Adamson *et al.* (1964) studied the effects of acute and total anoxia on newborn rhesus monkeys and showed that they develop primary apnoea which is followed by gasping and secondary apnoea. Those in secondary apnoea could be resuscitated only by expansion of the lungs with positive pressure ventilation. By analogy, human infants who are apnoeic at birth have been categorized as being in primary or secondary apnoea (Dawes 1968). This classification has led to a common assumption that infants who are apnoeic at birth and require resuscitation by intubation and positive pressure ventilation have been subjected to hypoxia during labour and/or delivery. In parallel with this assumption has been an increasing tendency to use the term 'asphyxia' in a biochemical rather than a clinical sense. For example, Towell (1976) states that 'asphyxia is defined as depletion of oxygen and accumulation of carbon dioxide leading to a state of acidosis which, during intrauterine life, is due to interference with placental gaseous exchange'. At the same time, other authors have equated very low Apgar scores (with the concomitant need for resuscitation by intubation and ventilation) with 'asphyxia' (Addy 1982).

As a result of these different views of birth asphyxia, many clinicians have come to accept that babies who do not breathe spontaneously at birth are 'asphyxiated' and must therefore be hypoxic and acidotic, without any objective evidence that this is the case. A similar problem has arisen over the definition of 'fetal distress' (Steer 1982) which is often diagnosed solely on the basis of the continuous fetal heart rate tracing as produced by a cardiotocograph, despite the

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knowledge that even with severely abnormal traces only about 50% of fetuses will have a significant acidosis (Beard *et al.* 1971). For example, Sykes *et al.* (1983) have shown that many forceps deliveries were performed for 'fetal distress' only to find that the baby was not acidotic and had normal Apgar scores at delivery. On the other hand, some babies had an acidosis despite a normal cardiotocogram (CTG). They also found a poor relation between 1-min Apgar scores and acid base measurements in cord blood (Sykes *et al.* 1982).

To help clarify this situation, we studied a consecutive series of infants born over a 6-month period at St Mary's Hospital, London who required intubation and ventilation, and determined the relation between the need for this intervention, cardiotocogram abnormalities in labour, and umbilical artery blood gas and pH values. We also looked at other factors which may have contributed to the need for intubation at birth.

Patients and methods

Over a 6-month period from February to July 1983, all 56 infants of 32 weeks gestation and above and weighing more than 1·5 kg who were resuscitated at birth by endotracheal intubation were studied. Infants of less than 32 weeks gestation were excluded as many of them were intubated electively.

The need for resuscitation was assessed by the paediatrician attending the delivery. Infants were intubated at 1–2 min of age if they were apnoeic with a heart rate of <100 beats/min and falling, or if they failed to respond to artificial ventilation with bag and mask (Lissauer 1982). Any thick meconium present at delivery was aspirated from the infant's mouth immediately after the delivery of the head, and the infant was intubated electively and any meconium in the trachea aspirated. Aspiration of the mouth was not performed routinely.

The CTG trace was analysed by one of us (P.J.S.) without knowledge of the outcome and classified as normal or abnormal. The CTG trace was considered normal if, antenatally or in the first stage of labour, the baseline rate was 120–160 beats/min with normal baseline variability (5–15 beats/min), reactive at least 20% of the time (with accelerations and fetal movement detected) and no decelerations were detected. The trace was also considered normal in the first stage of labour if there were decelerations but these were not >40 beats/min amplitude and any lagtime did not exceed 15 s. In the second stage of labour, decelerations >40 beats/min were accepted as normal provided they were early or variable but not late, and the baseline rate and variability between decelerations were normal. Any trace not conforming to these criteria was classified as abnormal. No attempt was made to assess the presence, absence or severity of hypoxia by CTG analysis.

Results

During the 6 months of the study 56 infants over 32 weeks gestation were intubated (4·3 per 100 births of this gestation). Eight were born by elective caesarean section and all of these had had normal antepartum CTG traces. Of those who were born after labour, 24 had a normal intrapartum CTG and 17 had an abnormal CTG. For seven infants the traces could not be classified: in four no CTG was performed (in two because of precipitate delivery), two were of poor technical quality, and one trace could not be categorized.

The umbilical artery pH and base deficit values are shown in Fig. 1. The pH was significantly lower and the base deficit significantly higher in the group with an abnormal CTG ($P<0{\cdot}01$, Wilcoxon rank sum test). Similarly the cord $P_a\text{O}_2$ values were significantly lower in the group with an abnormal CTG ($P<0{\cdot}01$, Wilcoxon rank sum test) although there was more overlap between the two groups than was shown by the pH values (Fig. 2). There was no significant difference in $P_a\text{CO}_2$ between the two groups.

Gestational age was not significantly different between babies with normal or abnormal CTG traces (Table 1). However, the mean birthweight was significantly lower in the group with abnormal CTG traces ($P<0{\cdot}005$, *t*-test). Correspondingly, the proportion of infants whose weight for gestational age was less than the 25th centile was significantly greater in the group with abnormal traces ($P<0{\cdot}0005$, χ^2 test with Yates' correction).

The Apgar scores at 1 min were not significantly related to the CTG classification whereas the 5-min score was significantly lower in the group with abnormal traces ($P<0{\cdot}05$, one-tailed Wilcoxon rank sum test) (Fig. 3).

All infants were reviewed with regard to neo-

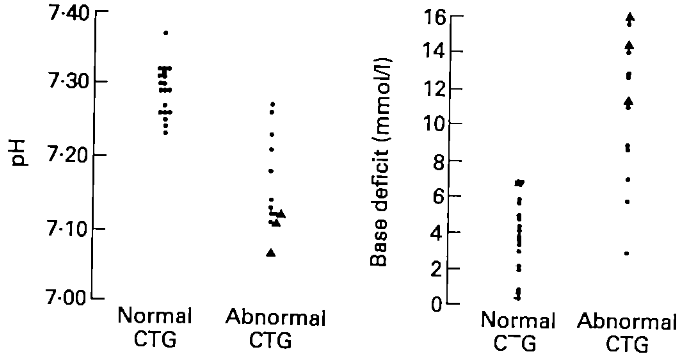

Fig. 1. Relationship between cardiotocogram (CTG) traces and umbilical artery pH and base deficit. Hypoxic-ischaemic encephalopathy: (●) absent; (▲) present.

natal complications. One infant with broad bone oestogenesis imperfecta died. None of the other 31 infants in the group with normal CTG traces had any neurological complications or any other subsequent clinical abnormalities. Eleven were admitted to the neonatal unit and the principal reason for admission has been listed in Table 2.

Of the 17 babies with abnormal CTG traces, five were admitted to the neonatal unit. Three had neurological complications, including convulsions and abnormalities on EEG and intracranial ultrasound. Two have developed spastic diplegia and one a hemiplegia.

Of the seven babies with unclassifiable CTG traces, two were admitted to the neonatal unit. One had retained lung liquid. The other had meconium aspirated from the trachea via the endotracheal tube at birth. Although no positive pressure ventilation was used, he developed a pneumomediastinum, became profoundly hypotensive and had convulsions. On follow-up he has a hemiplegia.

Resuscitation in infants with a normal CTG trace

The majority (32) of infants resuscitated at birth had no evidence of intrapartum hypoxia on the CTG trace, nor was there any evidence of hypoxia or acidosis on cord blood analysis when this was performed. In eight of these infants the indication for intubation was thick meconium at delivery and in the remaining 24 it was failure to establish breathing, with a heart rate <100

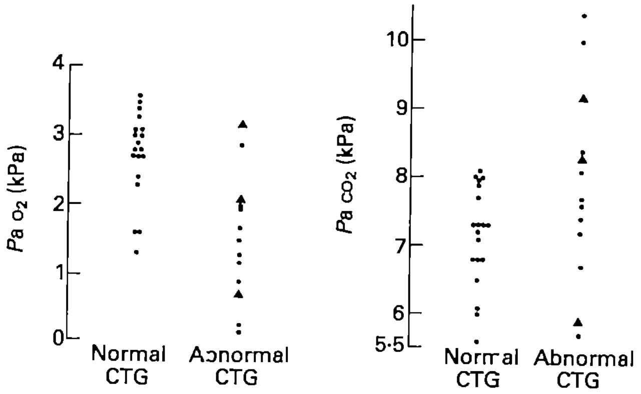

Fig. 2. Relationship between cardiotocogram (CTG) traces and umbilical artery P_{O_2} and P_{CO_2}. Hypoxic-ischaemic encephalopathy: (●) absent; (▲) present.

Table 1. Characteristics of 49 infants with normal or abnormal cardiotocograms (CTG) intubated at birth

Variable	Normal CTG ($n = 32$)	Abnormal CTG ($n = 17$)	*P* value
Mean (SD) birthweight (kg)	3·7(0·67)	2·9(0·54)	<0·005
Mean (SD) gestation (weeks)	39·1(2·5)	39·7(2·3)	n.s.
Weight for gestational age			
Centile <25	25·0%	65%	<0·0005
<10	12·5%	35%	
<5	9·4%	24%	

beats/min at 1–2 min of age. These latter infants may have required intubation because of the mode of delivery, anaesthetic or analgesic agents given to the mother, a tight nuchal cord, or trauma to the infant at delivery. Some of these possibilities are considered below.

Sixteen (66%) of these 24 infants were born by caesarean section, eight as an emergency and eight at elective operations. Two of the eight born vaginally were born by forceps and one by the breech. Only five had a spontaneous vaginal cephalic birth, two of whom had shoulder dystocia resulting in delay in delivering the infant and one infant's breathing was compromized because of osteogenesis imperfecta.

Thirteen women had a general anaesthetic, all for delivery by LSCS. Three of those delivered by LSCS had an epidural anaesthetic, as did the two delivered by forceps, the breech delivery and one vaginal cephalic delivery. In all patients with epidural anaesthesia for caesarean section lateral tilt was used to prevent aortocaval obstruction. Pethidine had been administered within 4 h of delivery in only two women, both delivered vaginally.

Each newborn was examined carefully by the paediatrician for evidence of birth trauma. A pronounced caput was present in three of the six infants born by LSCS for failure to progress in labour and in one born vaginally.

Resuscitation in infants with an abnormal CTG trace

Of the 17 infants with an abnormal CTG, additional factors which may have contributed to poor condition at birth are shown in Table 3. Ten (59%) were born by emergency LSCS, one by the breech and three by forceps. Only three were born by normal vaginal delivery. Often more than one factor was present which may have contributed to the need for intubation.

Discussion

Birth 'asphyxia' has been identified in the past by a number of different criteria. These include the

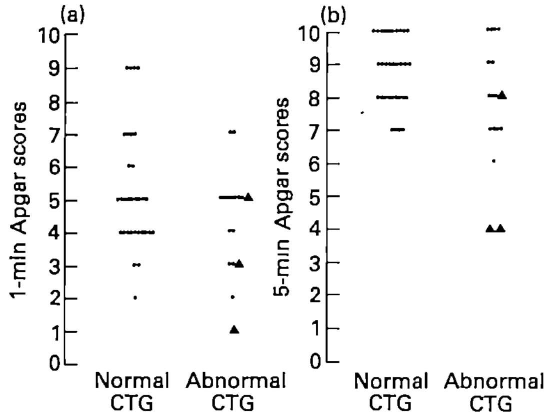

Fig. 3. Apgar scores according to cardiotocogram (CTG) traces (a) 1 min; (b) 5 min. Hypoxic-ischaemic encephalopathy: (●) absent; (▲) present.

Table 2. Principal reason for admission to the neonatal unit in 11 infants with normal and 7 with abnormal cardiotocograms (CTG)

Normal CTG	
Preterm	
Preterm	2
Preterm + hyaline membrane disease	2
Preterm + group B β-haemolytic streptococcal infection	1
Term	
Retained lung fluid	4
Pneumonia at 24 h	1
Broad bone osteogenesis imperfecta	1
Abnormal CTG	
Term	
Hypoxic-ischaemic encephalopathy with convulsions and neurological abnormalities	3
Mild meconium aspiration and persistent fetal circulation	1
Small-for-gestational age (birthweight 1·58 kg)	1
Unclassifiable CTG group	
Term	
Meconium aspiration, pneumomediastinum, shock and neurological abnormalities	1
Retained lung fluid	1

need for resuscitation, a low Apgar score, metabolic acidosis on cord blood analysis, or the development of hypoxic-ischaemic encephalopathy in the infant. In addition, cardiotocography is widely used as a screening system to detect cases of potential intrapartum hypoxia which if prolonged may result in birth asphyxia.

The Apgar score is widely used to assess the infant's condition at birth, although it has been criticized for being highly subjective. In our infants requiring resuscitation, the Apgar score at 1 min did not correlate well with the results of CTG trace or cord blood analysis. Sykes *et al.* (1982) also found a poor correlation between acidotic cord umbilical artery blood samples and Apgar scores at 1 min, and our findings support their assertion that the Apgar score is a poor guide to the presence or absence of acidosis. However, the 1-min Apgar score has practical value as a guide to the need for resuscitation of the newborn infant. Delayed response to resuscitation with low Apgar scores at 5, 10 and 20 min is known to be more predictive of long-term neurological handicap than a low score at 1 min (Nelson & Ellenberg 1981). In this study, two of the four infants with long-term neurological deficits had low 5-min Apgar scores.

The need for resuscitation at birth has been used to identify infants with more profound and prolonged depression. In 447 consecutive term infants requiring more than 1 min of positive pressure ventilation before sustained spon-

Table 3. Factors contributing to poor conditions at birth in 17 resuscitated infants with abnormal cardiotocograms

	Mode of delivery			
Contributory factors	Emergency LSCS ($n = 10$)	Breech ($n = 1$)	Forceps ($n = 3$)	Normal vaginal ($n = 3$)
General anaesthetic	6	—	—	—
Epidural	5	—	2	—
Pethidine	2	—	1	—
Caput	5	—	2	1
Cord prolapse	1	—	1	—
Tight nuchal cord	1	—	—	2
Thick meconium	3	—	2	3
Birthweight <10th centile	3	1	1	1

taneous respiration the mortality was increased more than a 100-fold (MacDonald *et al.* 1980). The need for intubation and positive pressure ventilation might therefore be expected to correlate more closely with acidosis at delivery than the Apgar score at 1 min. In fact, in our study, in more than half the infants requiring ventilation there was no evidence of acidosis.

Intrapartum CTG analysis is widely used as a screening method to detect intrapartum hypoxia, which may lead to acidosis (Howie 1986). For example, late decelerations are thought to result predominantly from hypoxaemia (Myers *et al.* 1973; Harris *et al.* 1982), and lead on to acidosis in between 25 and 50% (Low *et al.* 1981*a*). On the other hand, less than 2% of babies with a normal CTG trace are found to be acidotic on fetal blood samples and pH estimation (Beard *et al.* 1971). Thus, CTG analysis is a useful screening test for acidosis with a low false negative rate, but when the CTG is abnormal the presence or absence of hypoxia/acidosis can only be assessed by direct measurement, either of fetal blood samples in labour or cord blood samples at delivery. In common with most authors, in this study we have chosen to use cord artery rather than vein blood samples to assess blood gas/pH status at birth as being more directly representative of the fetus.

As brief episodes of hypoxia are common in labour, substantial short term fluctuations in $Pa\,O_2$ and $Pa\,CO_2$ can occur. Thus we were not surprised at the considerable overlap of $Pa\,O_2$ values in the groups with normal and abnormal CTG, and the lack of a significant difference in $Pa\,CO_2$ levels. In contrast, the pH and base deficit showed a closer correlation with CTG classification.

The relation between severe acidosis at delivery and outcome is currently not well understood. The incidence of motor and cognitive defects at 1 year of age increases with severity of metabolic acidosis at delivery, especially if there has been intrapartum hypoxia lasting >1 h (Low *et al.* 1984). In our study, three of the four infants with known long-term neurological deficit had proven abnormal acid-base status at delivery.

Although the majority of infants in this study who required resuscitation did not have evidence of intrapartum hypoxia, other factors were present to account for their need for intubation at birth. Most had an abnormal mode of delivery, with the majority being born by caesarean section. In these infants, the thoracic gas volume at birth is lower than in infants born vaginally (Boon *et al.* 1981), probably due to unresorbed lung fluid within the lungs, and this is likely to contribute to the need for intubation and ventilation.

Respiratory depression in newborn infants may result from anaesthetics or analgesics given to the mother. Pethidine was not a major cause of respiratory depression in this study, as only five woman received it.

The condition of the infant at birth depends not only on the degree of hypoxia to which it is exposed during labour, but on its ability to cope with hypoxia. Our study confirms the association between abnormal CTG in labour, acidosis at delivery, and low weight for gestational age, which has been widely reported by others (Low *et al.* 1981*b*).

Abnormalities of the respiratory system can also be an important factor in the need for intubation. Several of the infants in the study were preterm and developed respiratory distress syndrome, and one had multiple rib fractures from osteogenesis imperfecta.

As well as the tendency to consider infants requiring intubation at birth as hypoxic, when many of them are not, there is also a tendency in the absence of cord blood gas values to underestimate the extent to which the condition of a hypoxic infant may deteriorate in the hours after birth. For example, one of the infants in the study who developed long-term neurological damage had an abnormal umbilical artery blood gas analysis at birth (pH 7·08, base deficit 11·8 mmol/l) but despite active respiratory and cardiovascular support his condition deteriorated so that by 2 h of age his arterial blood pH was only 6·88 and the base deficit had risen to 26 mmol/l. If the cord blood acid-base analysis had not been available, the extent of his deterioration after birth would certainly not have been appreciated.

It is clear from our study that the need for intubation cannot be equated directly with previous intrapartum hypoxia, or metabolic acidosis at delivery. It follows that the use of the term 'birth asphyxia' to describe babies who do not establish spontaneous ventilation after birth should not be taken to imply an acid-base disturbance. Such disturbance can only be implied by the presence of a CTG abnormality in labour or preferably demonstrated by abnormal cord blood gas and pH values. We would therefore recommend that any baby requiring resuscitation at birth should have blood acid-base measurements made as a baseline from which to assess subsequent progress.

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Fetal distress during labour in diabetic pregnancy

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Summary. The frequency of fetal distress in labour was studied in 46 diabetic women and in 46 non-diabetic matched controls. Fetal distress was assessed by electronic fetal heart rate (FHR) monitoring and fetal scalp blood pH determinations in late first stage of labour. Ominous FHR and/or low pH (<7·26) was more common in the diabetic group than in the control group (17·4% and 10·9%, respectively) but the difference was not statistically significant. The frequency of caesarean section and low Apgar score at 1 min was significantly higher in the diabetic group ($P<0·05$). There was no correlation between maternal blood glucose regulation and the occurrence of fetal distress in the diabetic group. The results suggest that fetal distress may be slightly more common in labour in diabetic women compared with controls managed in a similar way. Careful FHR monitoring and liberal use of fetal scalp blood pH determinations is recommended.

It is debatable whether the fetus of a diabetic woman runs a greater risk of developing hypoxia and acidosis during labour than the fetus of a non-diabetic healthy woman. The elevated catecholamine levels found in newborns of diabetic mothers might be subsequent to fetal acidosis in labour (Hertel *et al.* 1982).

Maternal hyperglycaemia, associated with impaired fetal outcome (Pedersen 1977), might affect the fetal acid-base balance. Firstly, the placenta consumes glucose and produces lactate at a high rate (Hay & Sparks 1985). The placental lactate production is a normal aerobic process and primarily not a result of oxygen deficit. The glucose consumption is directly related to maternal blood glucose concentration, whereas the relation to lactate production is not well defined in man. It is known from animal experiments that approximately 60% of lactate production enters the fetal circulation (Hay & Sparks 1985). In diabetic women with hyperglycaemia, excess glucose and probably also excess lactate enters the fetus and might be of importance during periods of hypoxia (Datta & Kitzmiller 1982; Hay & Sparks 1985). Furthermore, severe hyperglycaemia in the sheep has been found to increase plasma lactate, leading to fetal acidosis, even in well-oxygenated fetuses (Robillard *et al.* 1978).

Secondly, maternal hyperglycaemia increases the concentration of glycosylated haemoglobin, mainly HbA_{1c} (Ditzel 1979), which has an increased oxygen affinity (Bunn & Briehl 1970). Elevated levels of glycosylated haemoglobin are suspected of reducing the availability of oxygen in peripheral tissue and occasionally cause hypoxia (Ditzel 1979). Together with the increased haemoglobin-oxygen affinity the oxygen saturation and tension are impaired, and an impaired maternal oxygen release in the uteroplacental circulation could perhaps cause fetal hypoxia and acidosis (Madsen & Ditzel 1982, 1984).

These potentially hazardous factors could be present but undetected in pregnancy, and then appear during the stress of labour. The purpose of this study was to elucidate the effects of labour on the fetus of the diabetic woman. The possible adverse influence of intervention in intrapartum

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management was equalized as far as possible by matching the study cases to non-diabetic controls.

Subjects and methods

The study was prospective and comprised a consecutive series of 46 diabetic women who were to be delivered vaginally and 46 non-diabetic women as controls. Five of the diabetic women were White class A (3 gestational diabetes), 5 class AB (3 gestational), 16 class B, 5 class C, 12 class D and 3 class F. Metabolic control during pregnancy included daily determinations of fasting and 3–4 preprandial blood glucose determinations with reflectance meter. The mean blood glucose concentration in the third trimester was calculated for each woman.

The antenatal fetal surveillance included nonstress test (NST) which was performed daily in in-patients and 1–2 times weekly in out-patients from the 30th week of gestation. Altogether 1182 NSTs were performed in the 46 diabetic pregnancies.

Labour was induced at 38 or 39 weeks gestation if spontaneous labour had not already occurred. The women were fasted on the day of delivery and given a 5·5% glucose infusion intravenously (90–120 ml/h).

The fetal heart rate (FHR) was continuously monitored by a scalp electrode in all patients. Uterine activity was monitored by a tocodynamometer in 22 and by an intrauterine open-end catheter in the other 24. Ominous FHR patterns fulfilled one or more of the following criteria (Beard *et al.* 1971; Ingemarsson 1981): (i) repeated late decelerations; (ii) repeated combined decelerations (combinations of early/variable and late decelerations); (iii) at least two of the following: tachycardia (>150 beats/min), silent pattern (variability <5 beats/min), ominous decelerations; and (iv) bradycardia (<110 beats/min) and loss of baseline variability and/or ominous decelerations.

Fetal scalp blood was sampled for pH determination in late first stage of labour (cervical dilatation 5–10 cm). Maternal capillary blood was simultaneously sampled to identify maternal acidosis. A fetal pH ≥7·26 was considered normal, 7·25–7·21 pre-acidotic, and ≤7·20 acidotic.

At birth, the umbilical cord was immediately clamped and blood sampled for pH determination. A cord artery blood pH ≤7·15 or a vein blood pH ≤7·20 was considered acidotic.

Data about pregnancy, delivery and the early neonatal period are collected in special records for all women giving birth in our department (Ingemarsson 1981). This research archive contains 23 734 cases. Routine electronic FHR monitoring during labour has been used since 1977 (Ingemarsson 1981). Fetal scalp blood pH determinations in the first stage of labour has been obtained in 3·3–11·4%.

Forty-six non-diabetic healthy women were selected from the archive for case-control matching. All had attended the public centres for antenatal care, and were considered to have uncomplicated pregnancies. NSTs were not performed in this group. The following criteria were used for the case-control matching: (i) maternal age ±5 years; (ii) parity; (iii) gestational age at delivery ±2 weeks; (iv) type of labour, matching women with spontaneous, induced or augmented labour; (v) fetal scalp blood pH determination at the same cervical dilatation (even for repeated samples); and (vi) epidural block.

When selecting the controls for matching of induced labours only indications not associated with fetal compromise, e.g. pelvic arthropathy, social indication, etc., were chosen. Intrapartum fetal surveillance was performed in the same way as in the diabetic group. All women in labour were managed by hospital staff obstetricians only, usually one of the authors, and had a high degree of homogeneity.

Results

The mean blood glucose concentration obtained in the third trimester in the diabetic pregnancies was 4·48 mmol/l (SD 0·83, range 3·1–7·2). The calculations were made from a total of 6075 determinations (mean number/woman 135, range 29–552). Values were not available in one woman, but the HbA_{1c} was normal. There was no difference in blood glucose values between patients who developed fetal distress in labour (ominous FHR, fetal acidosis or pre-acidosis, cord blood acidosis, or Apgar score <7) and those who had an uneventful labour (unpaired *t*-test). Only one of six women delivered by a caesarean section for suspected fetal distress had a mean blood glucose concentration above 5·0 mmol/l.

Comparison of the obstetrical and neonatal variables in the diabetic and the control group

(Table 1) shows that on average, the diabetic women were delivered 1 week earlier than the controls, but the mean infant birthweight was 3501 g compared with 3361 g. Other variables were similar.

Further obstetrical data (Table 2) show that the incidence of ominous FHR patterns in the diabetic group was twice that in the control group, but the difference was statistically not significant (McNemar test). The mean fetal scalp blood pH was 7·34 (SD 0·08) in the diabetic group; six fetuses had a pH ≤7·25. In one patient, fetal pre-acidosis coincided with maternal acidosis. Corresponding mean pH in the control group was 7·34 (SD 0·04) and two fetuses had a low pH. The difference was statistically not significant (McNemar test).

Altogether 63 fetal scalp blood pH determinations were performed in each group, including repeat samples in 17 patients because of ominous or suspicious FHR patterns or prolonged first stage of labour. A statistical analysis of the 2×63 pH values revealed no significant difference between the diabetic and the control group (Wilcoxon's signed-rank test).

The diabetic women with low pH values were equally distributed into the different White classes, although ominous FHR patterns occurred in classes B-F only.

Comparison of the mode of delivery (Table 2) shows that the frequency of instrumental delivery was the same in the two groups, 19·6% in the diabetic (4 vacuum extractions and 5 forceps) and 21·7% in the control group (9 vacuum extractions and 1 forceps). Suspected fetal distress as an indication for instrumental delivery was equally common in both groups; 10·9%. Section was performed in 17·4% in the diabetic group, compared with zero in the control group (McNemar test; $P<0{\cdot}05$). Of eight sections in the diabetic group, six were done for fetal distress (three having both ominous FHR and low pH) and two for cephalopelvic disproportion.

The frequency of low Apgar score at 1 min (<7) was 10·9% in the diabetic group and zero in the control group (McNemar test; $P<0{\cdot}05$). Only one infant had a low score at 5 min, this was an infant in the diabetic group. Three of the five infants with a low Apgar score were born either by section or instrumentally.

Cord blood pH was determined in 26 patients in the diabetic group and in 16 in the control group. Cord blood acidosis occurred in 26·9% in the diabetic group but in none of the control group. In the diabetic group, signs of fetal distress were present in four of the seven cases with low cord pH. No correlation was found between cord blood pH value and the mode of delivery or Apgar score. Only one infant had both a low Apgar score and a low cord blood pH.

Discussion

A pregnant woman identified as having diabetes attracts considerable attention by the obstetri-

Table 1. Obstetrical and neonatal data showing the comparison between the 46 diabetic women and the non-diabetic matched controls*

Characteristics	Diabetic women (*n* = 46)		Non-diabetic controls (*n* = 46)	
Maternal age* (years)	26·5	(3·9)	27·0	(4·2)
Primiparous*	27	(58·7%)	27	(58·7%)
Gestational age at delivery* (weeks)	38·7	(1·4)	39·7	(2·1)
Labour induction*	29	(63·0%)	29	(63·0%)
Oxytocin administration*	39	(84·8%)	39	(84·8%)
Epidural block*	30	(65·2%)	30	(65·2%)
Membrane rupture to delivery interval (h)	7·2	(4·6)	8·2	(5·6)
Length of second stage (h) (caesarean sections excluded)	0·93	(0·84)	1·16	(0·99)
Preterm delivery (<37th week)	2	(4·3%)	4	(8·7%)
Birthweight (g)	3501	(572)	3361	(701)
Small-for-gestational age (<−2 SD)	2	(4·3%)	2	(4·3%)
Large-for-gestational age (>+2 SD)	5	(10·9%)	3	(6·5%)

* Matched criteria are marked with an asterisk·
Results are shown as means (SD) or *n*(%) as appropriate.

Table 2. Incidences of suspected fetal distress and mode of delivery in the 46 diabetic women and the non-diabetic matched controls

	Diabetic women ($n = 46$)	Non-diabetic controls ($n = 46$)	
	n (%)	n (%)	P-value*
Fetal distress			
Ominous FHR	6 (13·0)	3 (6·5)	NS
Fetal pH 7·25–7·21	5 (10·9)	2 (4·3)	NS
Fetal pH ≤7·20	1 (2·2)	0 (—)	
Ominous FHR and/or low fetal pH	8 (17·4)	5 (10·9)	NS
Mode of delivery			
Spontaneous	29 (63·0)	36 (78·3)	
Instrumental†, total	9 (19·6)	10 (21·7)	
For fetal distress	5 (10·9)	5 (10·9)	$P<0·05$
Caesarean section, total	8 (17·4)	0 (—)	
For fetal distress	6 (13·0)	0 (—)	
Apgar score (<7)			
1 min	5 (10·9)	0 (—)	$P<0·05$
5 min	1 (2·2)	0 (—)	NS

FHR, Fetal heart rate.

* The McNemar test was used for statistical analyses.

† Vacuum extraction or forceps.

cian during pregnancy and labour. As a consequence, she tends to be exposed to an interventional obstetric policy with a high rate of induced labours, caesarean sections and instrumental deliveries of fear for fetal and maternal complications. This interventional policy in diabetic pregnancy might be disadvantageous, particularly in induced labour with an increased risk of fetal acidosis due to uterine hypertonus with decreased utero-placental perfusion or prolonged labour (Schifrin 1972; Martinsen *et al.* 1982). Abnormal FHR patterns and low fetal pH are associated with epidural block due to maternal hypotension or as a direct toxic effect on the fetus by the anaesthetic agent (Schifrin 1972; Willcourt *et al.* 1982). In the present study, comparing diabetic women with non-diabetic controls, such interventions were therefore matched for. The matching criteria also included parity, since prolonged labour and cord blood acidosis occur more often in first labours (Martinsen *et al.* 1982).

In the present series of 46 diabetic women there was a high rate of labour induction (63·0%), augmentation of labour (84·8%) and epidural block (65·2%). Although the mean gestational age at delivery was 1 week shorter in the diabetic group, this could not have affected the comparison because preterm delivery, mean birthweight and size for gestation were similar.

The frequencies of ominous FHR pattern and low fetal scalp blood pH were consistently higher in the diabetic group, but the differences were statistically not significant (Table 2). Significant differences were found only for the mode of delivery and for the frequency of a low Apgar score at 1 min. The rate of caesarean section was 17·4% and that of low Apgar score 10·9% in the diabetic group compared with zero for both variables in the control group. Owing to the matching procedure, concomitant factors with occasionally adverse effects were operating also in the control group. The differences found in the present study thus suggest that the fetal resistance and tolerance to the stress of labour might be impaired in diabetic pregnancy in women selected for vaginal delivery.

The high rate of cord blood acidosis in the diabetic group (26·9%) compared with the control group (zero) further supports this suggestion although the correlation of cord blood pH with the mode of delivery and with the Apgar score was poor. A higher rate of cord blood acidosis has been reported in diabetic pregnancies compared with controls (Hertel *et al.* 1982).

Stressful maternal metabolic changes during pregnancy may condition the fetus to react excessively with elevated catecholamine levels and distress during the strain of labour (Artal *et al.* 1982), but no correlation was found in the present study between mean blood glucose concentration and the occurrence of fetal distress. Thus, the results suggest a slightly increased risk for fetal distress in labour for the diabetic woman. Careful monitoring of the FHR and liberal use of fetal scalp blood sampling for pH determination is recommended.

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Early conceptual loss in subfertile patients

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Summary. The incidence of early conceptual loss was studied in 27 subfertile women by measuring their serum and urine hCG levels in the luteal phase. Eleven patients eventually had clinically confirmed pregnancies, nine of whom had had significant hCG elevations in previous menstrual cycles. In the remaining 16 patients, who have so far failed to achieve a clinical pregnancy, only three had had elevated hCG results. Thus 'apparent' early conceptual loss in non-pregnancy cycles was found to be more often associated with the fertile group of patients.

Among the subfertile population there is always a group who, despite appropriate investigation, seem to have no apparent bar to conception. There are also those who despite correction of an identifiable problem remain infertile.

It is possible that such patients may not have an inability to conceive but may have an inability to retain an early conception. Inability to retain an early conception is commonly demonstrated in patients receiving embryo transfer following in-vitro fertilization. Apart from those patients receiving embryo transfer, the occurrence of subclinical abortion has been shown by the presence of transient spikes of human chorionic gonadotrophin (hCG) during the luteal phase in normally fertile patients (Miller *et al.* 1980; Edmonds *et al.* 1982; Whittaker *et al.* 1983), in patients receiving clomiphene citrate (Braunstein *et al.* 1977; Ho & Tang 1982) and in patients with intrauterine contraceptive devices (Beling *et al.* 1976; Hodgen *et al.* 1978; Orloff *et al.* 1979; Landesman *et al.* 1976). Subclinical abortion has also been shown by the presence of Schwangerschaftsprotein 1 (SP_1) in a patient receiving exogenous hCG for ovulation induction (Ahmed & Klopper 1984).

The measurement of hCG was used in this study to see if recurrent subclinical abortion could be identified as a major reason for infertility.

Patients and methods

The occurrence of early conceptual loss was assessed in all women who attended the infertility clinic. They were to be monitored for up to six cycles (dependent on whether they became pregnant or not) in which there should be no bar to conception. No woman would receive human menopausal gonadotrophin (hMG) or hCG.

Twenty-seven patients were recruited (Table 1). The mean duration of infertility at the time of recruitment was 48 months. Nineteen patients were receiving clomiphene citrate (Clomid, Merrell, Hounslow, Middlesex) having demonstrated an inability to ovulate regularly (one or more luteal serum progesterone levels <35 nmol/l) and two of these patients were receiving artificial insemination with donor semen (AID). One patient was receiving AID alone and one was receiving artificial insemination with her husband's semen (AIH). One patient with hyperprolactinaemia was being treated with bromocriptine (Parlodel, Sandoz, Feltham, Middlesex). Five patients were receiving no treatment during the study (four were undergoing preliminary investigation and one had idiopathic infertility). Tubal patency and ovulation (serum progesterone >35 nmol/l) were con-

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Table 1. Treatment and duration of infertility of patients attending subfertility clinic

Treatment	No. of patients	Mean duration of infertility* (months)	Mean duration of treatment† (months)
Clomiphene citrate (± AID)	19	51	10
Bromocriptine	1	109	1
AID	1	52	3
AIH	1	51	1
No treatment	5	39	12

*Duration of infertility is the period of time between cessation of contraception or the last pregnancy and participation in the study.

†Duration of treatment is defined as the time from the start of treatment until participation in the study, or in the case of no treatment, from the date of 1st attendance at the clinic.

AID, Artificial insemination with donor semen.

AIH, Artificial insemination with husband's semen.

firmed in all patients. Apart form those patients receiving AID, the semen analyses of the partners of the patients were satisfactory (median sperm counts $>20\times10^6$/ml and $\geqslant10\times10^6$ motile sperm per ejaculate).

Early morning urine samples were collected an alternate days from day 19 of the menstrual cycles until menstruation. Serum samples were collected on days 21, 25 and 28. All samples were stored in aliquots at −20°C until analysed. In addition, control samples of blood and urine were obtained from 11 ovulatory patients at mid-cycle (recruited from the AID clinic) and from 32 postmenopausal patients.

Radioimmunoassay

A standard radioimmunoassay, with an accelerated second antibody technique, was used to measure hCG in urine and serum. The antiserum used was raised against the beta-subunit of hCG [SB6, kindly supplied by the National Institute of Child Health and Human Development and the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases (NIADDKD)]; the standards were calibrated against the 1st International Reference Preparation [obtained from National Institute of Biological Standards, Holly Hill, London] in pooled male urine or serum as appropriate. ^{125}I-whole hCG molecule (Preparation CR121, NIADDKD) was used as the tracer.

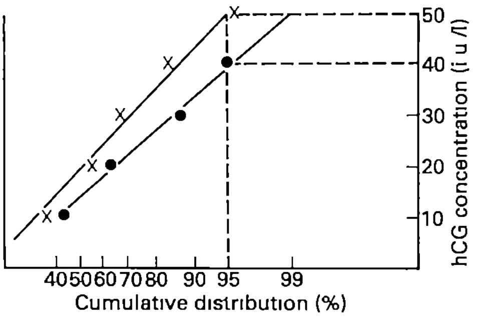

Fig. 1. Probability graph for hCG levels in control samples. (●) Serum samples; (x) urine samples

The minimum detection limit for both assays was 5 i.u./l. The interassay variation in the serum assay was 9·7% (sample with a mean level of 95 i.u./l hCG) and in the urine assay was 12·0% (sample with a mean level of 192 i.u./l).

Results

The control samples of serum and urine were assayed for hCG levels to determine a statistically relevant diagnostic level, above which conception was likely to have occurred. These results were plotted on probability graph paper. The hCG concentrations equivalent to the 95% cumulative distribution points were taken as the relevant 'cut off' levels for the diagnosis of trophoblastic activity (Fig. 1). These levels were 50 i.u./l for urine and 40 i.u./l for serum. Eleven of the 27 women achieved clinical pregnancies, which were detected by us at an early stage (only one by day 21 but the latest by day 31 from the last menstrual period), and the pregnancies were confirmed by a standard urine pregnancy test at 6 weeks gestation. Nine of these pregnancies continued, and two aborted spontaneously at 11 and 20 weeks.

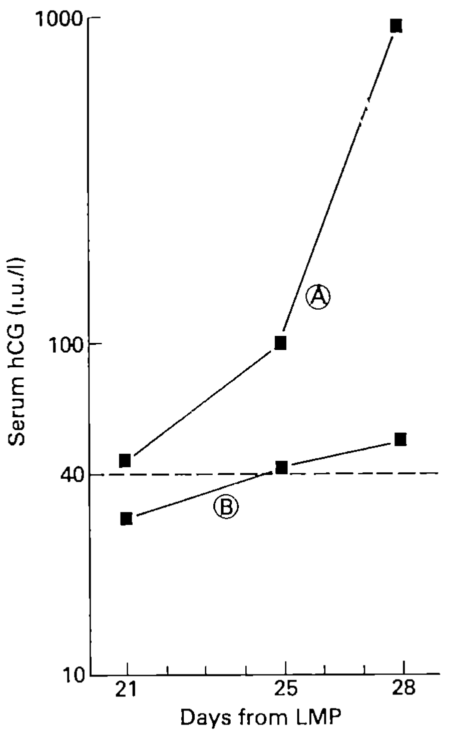

Fig. 2. The very early detection of a pregnancy by significant serum hCG results in one woman (cycle A). Day 21, 25 and 28 serum hCG results are shown for the same woman in a previous cycle (cycle B) when early conceptual loss was suspected and menstruation occurred on day 40. Note log scale on y axis.

One of the clinically confirmed pregnancies was detected in serum by day 21. This was in the only woman in whom early conceptual loss had been detected by serum hCG results (>40 i.u./l) during a previous cycle (Fig. 2) and the only woman in whom significant serum results preceded significant urine results. The suspected early conceptual loss was also shown with significant urine results. Significant urinary hCG levels (>50 i.u./l) were found in a total of 19 menstrual cycles other than 'confirmed pregnancy' cycles. They occurred in 9 of the 11 women who subsequently had clinically confirmed pregnancies and in only 3 of the 16 who did not.

In Fig. 3 are shown urine hCG results of two cycles (1) and (2), in which early conceptual loss was suspected. Cycles (3) and (4) followed (1) and (2) respectively and pregnancies were confirmed.

All 19 of the cycles with significant urine-detected hCG results (other than 'confirmed pregnancy' cycles) are summarized in Fig. 4. Each shaded square in Fig. 4 indicates each first day of detection of significant hCG; each unshaded square is a subsequent sample with significant hCG. Therefore, it can be seen that only half of the positive results on day 19 were followed by a significant result on day 21. Furthermore, as only one of our clinically confirmed pregnancies was detected by day 21, it suggests that positive results on days 19 and 21 may not be due to trophoblastic hCG production.

On the basis of the positive hCG results, the patients can be divided into four groups as shown in Table 2. χ^2 analysis of the results revealed an association between confirmed pregnancy and a history of 'apparent' early conceptual loss ($P<0{\cdot}01$, Fisher's exact test), which was not related to any treatment given (Table 3).

Study of those significant hCG results in the non-pregnant cycles (Fig. 4) revealed more positive findings on days 19 and 21 than one would have expected from early blastocyst hCG production. This led us to conclude that there were still false positive results close to the ovulatory period. Only one of the confirmed pregnancies could be detected by day 21 of the menstrual cycle. The later significant hCG results were more likely to be associated with early conceptual loss, especially when one result was supported by another 2 days later (Figs 2, 3 and 4). Therefore, we looked for an association between suspected early conceptual loss and pregnancy if results on days 19 and 21 and cycles with only one significant hCG result are con-

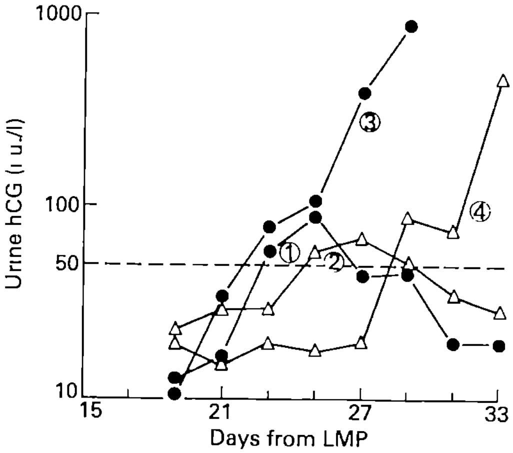

Fig. 3. Detection of significant urine hCG levels in two women on clomiphene for no-pregnancy confirmed cycles (1 and 2) followed by pregnancy confirmed cycles (3 and 4 respectively). Note log scale on y axis.

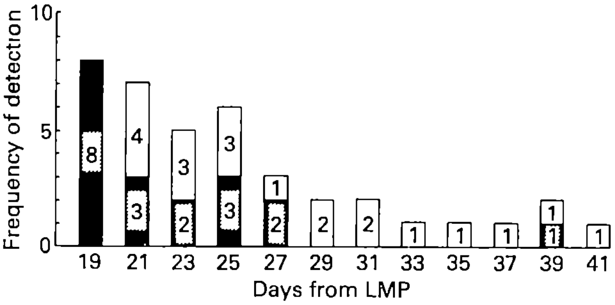

Fig. 4. Histogram of frequency of detection of urinary hCG levels (>50 i.u./l) when no subsequent pregnancy was confirmed The histogram shows the days on which the first significant hCG levels were detected and also where successive significant results were found (Therefore one cycle had a second positive result, four had a third, two had a fourth and one had a fifth, sixth and seventh) Total positive samples = 39; no of cycles = 19. (■) First day of detection (n = 19); (□) successive days of detection (n = 20).

sidered separately (Table 4). We found that there was still an association, with five very significant results remaining and all among the group of women who eventually became pregnant (5 out of 11 compared with 0 out of 16 non-pregnant). This was statistically significant (P<0·01) and showed that any loss was still likely to be associated with the more fertile group of women.

Cycle length

Only 11 cases of early conceptual loss out of the 19 were associated with a delay in menstruation of at least 48 h, but extension of the menstrual cycle was not always associated with significant hCG levels.

Discussion

The diagnostic 'cut-off' level of 50 i.u./l hCG (50 i.u./l 1st International Reference Preparation = 25 i.u./l 2nd International Standard) for urine samples and 40 i.u./l for serum samples were established to indicate significant production of hCG which would indicate that conception had taken place. This was based on the use of control samples with elevated pituitary gonadotrophin levels, which are known to cross-react with the antiserum used in the assay (Vaitukaitus *et al.* 1972; Vaitukaitis 1981; Edmonds *et al.* 1982). This antiserum has been well documented in the literature cited, as well as in many other scientific papers, because it has been raised against the beta subunit of hCG, has been readily available worldwide and has proved reliable. Recently, however, there has been concern over discordant hCG results with all types of hCG immunoassays, even those employing monoclonal antibodies (Hussa *et al.* 1985). These discordant results have been found to be due to the presence of altered forms of hCG, production of hCG-like substances in non-pregnant women (no tumours detected), luteinizing hormone and antibodies to hCG. These types of interference have caused us to establish what might seem rather high 'cut-off' levels. In addition, a recent report by Klopper & Ahmed (1985) showed that, by the application of low 'cut-off' levels for both SP_1 and hCG assays, too many false positive results are obtained, especially around the period of ovulation. We therefore applied *our* calculated levels to a group of subfertile women.

In our subfertile group, we found more biochemical evidence for early conceptual loss in those women who ultimately became clinically pregnant an association which was statistically significant.

In conclusion, significant hCG levels in non-pregnant cycles are more often found in the most fertile group of women attending an infertility clinic; but the results are probably a combination of those which are caused by real early conceptual losses and those which are an inseparable mixture of false positives and early conceptual losses. We have been unable to show so far that recurrent subclinical abortion could be a major reason for infertility. In fact the prog-

Table 2. Number of patients who became clinically pregnant, and whether or not they had 'apparent' early conceptual loss

	Clinical pregnancy achieved	No clinical pregnancy achieved	Total
No. with 'apparent' early conceptual loss	9	3	12
No. without evidence for early conceptual loss	2	13	15
Total	11	16	27

Table 3. Treatment of patients in the study and outcome

	Previous history of 'apparent' early conceptual loss		No previous history of 'apparent' early conceptual loss	
Treatment	No. of patients	Pregnancies	No. of patients	Pregnancies
Clomiphene citrate (+ AID)	9	6	10	1
Bromocriptine	1	1		
AID alone	1	1		
AIH alone			1	1
No treatment	1	1	4	0
Total	12	9	15	2

AID, Artificial insemination with donor semen.
AIH, Artificial insemination with husband's semen

Table 4. Table of number of patients who became clinically pregnant and whether or not they had at least two significant hCG results from day 23 onwards

	Clinical pregnancy achieved	No clinical pregnancy achieved	Total
No. with ≥ 2 significant hCG results from day 23	5	0	5
No. without	6	16	22
Total	11	16	27

χ^2 analysis of 2×2 contingency table revealed $\chi^2 = 6{\cdot}2$, $P<0{\cdot}13$; Fisher's exact test, $P<0{\cdot}01$, indicating an association between pregnancy and a previous history of 'apparent' early conceptual losses.

nosis for women showing significant elevations in hCG levels (non-pregnancy cycles) is very good.

Hertig *et al.* (1959) showed evidence of early conception occurring at a much higher rate than becomes clinically obvious by the detection of fertilized ova in fertile women. Our findings agree that conception was occurring more often than was clinically evident in the more fertile women attending our infertility clinic.

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Prostaglandin D_2 release by endometrium and myometrium

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Summary. Prostaglandin D_2 (PGD_2) release was studied using a superfusion technique in endometrium and myometrium obtained at hysterectomy from 36 women with measured menstrual blood loss (range 4–840 ml). PGD_2 was produced by both tissues with greater rates from endometrium. Cyclical changes in release were found only in the endometrium with increased rates during menstruation and the mid-luteal phase. In the myometrium the highest release rates were present during menstruation at the start of the superfusion. No significant correlation was found between menstrual blood loss and endometrial or myometrial PGD_2 release.

Prostaglandin production by non-pregnant human endometrium and myometrium has interested research workers for many years. Although prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostaglandin E_2 (PGE_2) and 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) have received considerable attention there is little information regarding prostaglandin D_2 (PGD_2) (Downie *et al.* 1974; Willman *et al.* 1976; Maathuis & Kelly 1978; Abel & Kelly 1979; Demers *et al.* 1984; Rees *et al.* 1984). PGD_2 is a vasodilator and inhibitor of platelet aggregation and is therefore a potential candidate in the control of menstrual blood loss (Flower *et al.* 1976; Smith 1980). Studies of luteal endometrium show increased PGD_2 synthesis in menorrhagic women (Smith *et al.* 1981), but there are few data at other phases of the menstrual cycle or from the myometrium.

The present study was therefore undertaken to explore endometrial and myometrial PGD_2 release *in vitro* throughout the menstrual cycle in women with normal (<80 ml) and excessive menstrual blood loss (≥80 ml) (Hallberg *et al.* 1966). A superfusion technique was used to allow measurement of PGD_2 release rather than its concentration in excised tissue which is considered to represent the capacity for formation in response to trauma rather than in-vivo tissue concentrations (Granström & Samuelsson 1978; Liggins *et al.* 1980; Rees *et al.* 1984).

Patients and methods

Patients

Endometrium and myometrium were obtained from 36 women at hysterectomy. The women were between 38 and 48 years of age, they had regular menstrual cycles of between 23 and 33 days, none had used either oral or intrauterine contraception or hormonal medication for at least 6 months before surgery and none had received prostaglandin synthetase inhibitors in the cycle preceding hysterectomy. Menstrual blood loss, estimated for two periods before the operation with the alkaline haematin method, ranged from 4 to 840 ml, with 10 women having a normal menstrual blood loss and 26 a heavy menstrual blood loss of ≥80 ml (Hallberg & Nilsson 1964; Hallberg *et al.* 1966). The stage of

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the cycle at which the tissue was obtained was determined from the patient's menstrual history, endometrial histology and plasma progesterone levels estimated by radioimmunoassay in peripheral blood taken at the time of surgery (Noyes *et al.* 1950; Turnbull *et al.* 1974). Nine specimens were obtained during menstruation, eight in the follicular phase, four in the early luteal phase, eight in the mid-luteal phase, and seven in the late luteal phase.

Tissue superfusion and PGD_2 measurement

Superfusion of endometrium and myometrium was performed as described previously (Rees *et al.* 1984). Briefly the tissues were minced, placed between membrane filters and Krebs buffer (containing 2 g/l glucose, saturated with 95% O_2 and 5% CO_2 at 37°C) pumped through at 0·6 ml/min for 5 h. Buffer samples were collected in 10-min fractions and PGD_2 concentrations measured by radioimmunoassay as described previously, employing an antiserum developed by one of us (R.W.K.) (Kelly *et al.* 1986). At the end of each superfusion the tissues were dried to constant weight and PGD_2 release was expressed in terms of ng/g dry tissue/min.

Preliminary experiments (n=6) in which all 10-min buffer fractions were assayed showed that PGD_2 release was high at the start of superfusion and fell during the first 3 h to reach a plateau that was maintained until the end of the 5-h superfusion. PGD_2 release rates were compared both at the start of the superfusion and at the plateau phase between 3 and 4 h after the start of superfusion. The former may reflect the total capacity for prostaglandin formation and the latter basal release rates after washout of trauma-induced PG release.

Tissue viability was confirmed by trypan blue dye exclusion, glucose uptake by the tissues and histological examination of formol fixed specimens.

Statistical analysis

Menstrual blood loss and PGD_2 release are not normally distributed so that log transformation was used to normalize the data which were then treated with parametric methods (one way analysis of variance followed by Student's *t*-test for comparison of several groups, least squares regression and the product moment correlation coefficient for examination of linear relation).

Results

PGD_2 was produced by both endometrium and myometrium with significantly greater amounts from the endometrium, both at the start and the plateau phase of the superfusion (Figs 1 and 2, P <0·001). Cyclical changes in PGD_2 release were found only in the endometrium with higher levels in the mid-luteal and menstrual phases than in the follicular phase (P<0·05, Fig. 1). In the initial phase the highest rates of release were found during the mid-luteal stage. In contrast PGD_2 release from the myometrium was significantly elevated at the start of the superfusion in tissues obtained during menstruation (P<0·05, Fig. 2). No correlation was found between total menstrual blood loss (range 4–840 ml) and PGD_2 release at any stage of the menstrual cycle from either endometrium and myometrium; but in

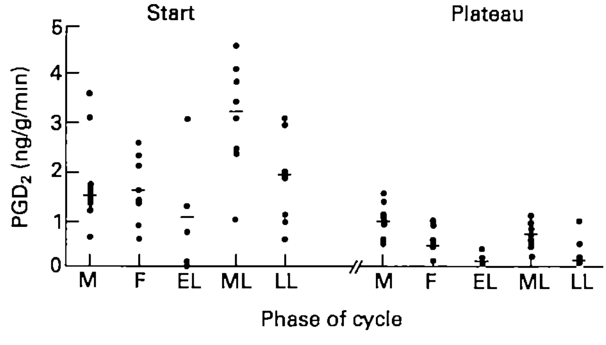

Fig. 1. Endometrial PGD_2 release. The bars represent median values. M, Menstrual; F, follicular; EL, early luteal; ML, mid-luteal; LL, late luteal phases of the menstrual cycle.

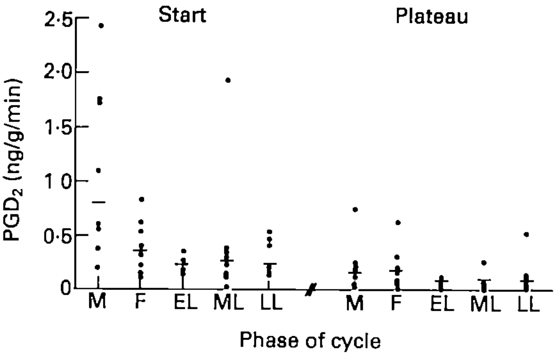

Fig. 2. Myometrial PGD_2 release. The bars represent median values. M, Menstrual; F, follicular; EL, early luteal; ML, mid-luteal; LL, late luteal phases of the menstrual cycle.

three uteri obtained during the first 2 days of menstruation when menstrual flow is greatest (Rybo 1966), a relation was evident between blood loss and myometrial PGD_2 release (Figs 3 and 4) at the start of superfusion.

Discussion

This study examined PGD_2 release *in vitro* by endometrium and myometrium obtained at different stages of the menstrual cycle from women with known menstrual blood loss; PGD_2 was produced by both tissues but release rates were significantly greater in endometrium. The same pattern has been found for the other prostaglandins $PGF_{2\alpha}$, PGE_2 and 6-keto-$FGF_{1\alpha}$ (Abel & Kelly 1979; Demers *et al.* 1984; Rees *et al.* 1984). The release rates of PGD_2 were lower than would have been expected from studies using chromatography of endometrial and myometrial arachidonic acid metabolites (Abel & Kelly 1979; Smith *et al.* 1981; Demers *et al.* 1984). The discrepancy may be due to either the different methods employed or interference by a substance with the same chromatographic mobility as PGD_2.

Cyclical changes in PGD_2 release were found only in the endometrium, with increased levels during the mid-luteal phase and menstruation. Similar changes have been found with other prostaglandins (Downie *et al.* 1974; Willman *et al.* 1976; Maathuis & Kelly 1978; Rees *et al.* 1984). In the myometrium the highest release rates were found at the start of the superfusion in tissue obtained during menstruation. This may be relevant to the control of menstrual bleeding

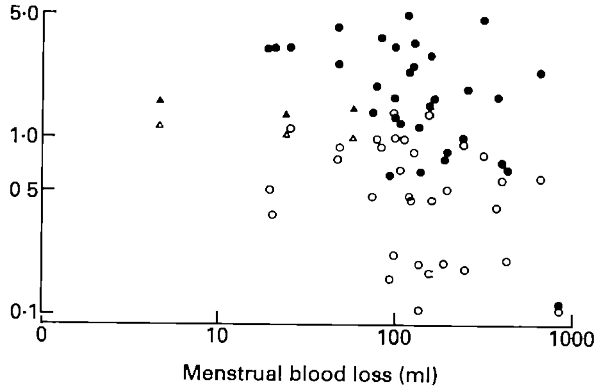

Fig. 3. Relation between menstrual blood loss and PGD_2 release in the endometrium at start of superfusion (●, ▲) and at plateau phase (○, △). The symbols △, ▲ represent the values for three specimens obtained during the first 2 days of menstruation

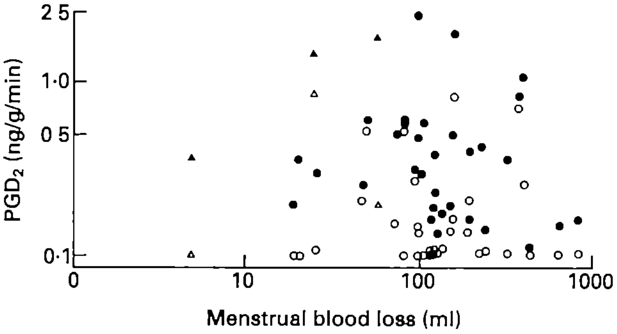

Fig. 4. Relation between menstrual blood loss and PGD$_2$ release in the myometrium at start of superfusion (●, ▲) and at plateau phase (○, △). The symbols △, ▲ represent the values for three specimens obtained during the first 2 days of menstruation.

since PGD$_2$ is a vasodilator and inhibitor of platelet aggregation and rates at the start of a superfusion include a trauma induced component (Flower *et al.* 1976; Smith 1980). Furthermore, the mass of myometrium is greater than that of the endometrium so that total PGD$_2$ production may be higher in the former tissue. Morphological studies indicate that platelet aggregation in menstrual endometrium is significantly less than that occurring in damaged vessels in other tissue (Christiaens *et al.* 1980). A possible cause may be the transfer of PGD$_2$ from the myometrium to the endometrium during menstruation.

No correlation was found between PGD$_2$ release in either endometrium or myometrium at any phase of the cycle and menstrual blood loss (range 4–840 ml). We are therefore unable to confirm the increased PGD$_2$ synthesis in menorrhagic women found in luteal endometrium (Smith *et al.* 1981). But the suggestion of a relation between blood loss and myometrial PGD$_2$ release in the first 2 days of menstruation may explain the efficacy of prostaglandin synthetase inhibitors taken during menstruation to reduce menstrual bleeding (Anderson *et al.* 1976). Thus any increased PGD$_2$ production during menstruation in patients with menorrhagia is not maintained throughout the menstrual cycle.

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Perinatal listeriosis. A report of six cases

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Summary. The clinical and pathological findings in six patients with perinatal listeriosis are presented. One pregnancy resulted in a liveborn infant who developed listerial septicaemia but made a complete recovery following prompt treatment. The other pregnancies ended in intrauterine death. Often antecedent maternal prodromal illness preceded expulsion of a macerated fetus by only a matter of hours making early diagnosis difficult. In all cases the diagnosis of listerial infection was apparent only after the birth of the fetus or new born.

Listeriosis is a considerable cause of perinatal morbidity and mortality (Barresi 1980; Bortolussi 1984) and the incidence of perinatal listeriosis within England and Wales appears to be increasing (Editorial 1985). This may reflect increased awareness of a condition which, until recently, had been underreported or underdiagnosed (Robertson *et al.* 1979; Editorial 1980). Within a 12-month period, there were six patients with perinatal listeriosis in two adjacent district general hospitals and we wish to describe their clinical, epidemiological and pathological findings to highlight their variable presentations and pathological features.

Clinical data

A summary of the clinical data of all six patients is given in Table 1.

Four of the pregnancies complicated by perinatal listeriosis terminated as mid-trimester abortions or early third trimester intrauterine deaths. The other two pregnancies proceeded until 38 weeks and term gestation, resulting in the delivery respectively of a stillborn infant and an infant with clinical signs of sepsis.

Patient 1.

This case report is illustrative of patients 1, 2, 3 and 4 (Table 1) in whom pregnancy resulted in intrauterine deaths.

A 23-year-old white European booked for antenatal care in September 1984 with 12 weeks amenorrhoea. Her previous obstetric history included a full term pregnancy in 1983 complicated by vaginal herpes, and a left tubal abortion in 1984. Her pregnancy was uneventful until she was admitted at 20 weeks gestation by dates with painful uterine contractions, absent fetal heart sounds and a cervix that was dilated to 2 cm. She gave a history of an influenza-like illness immediately preceding her admission. Abortion was induced and a macroscopically normal female fetus and placenta were delivered. Her temperature, which before abortion was 37·5°C, subsided following expulsion of the conceptus and she was discharged home well 48 h later.

Patient 5.

A 20-year-old white European primigravida booked at 20 weeks gestation for antenatal care in October 1984. Her previous antenatal care

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Table 1. Clinical details of six women with perinatal listeriosis

Clinical details	Patient no 1	2	3	4	5	6
Gravidity	3	2	1	1	1	1
Age (years)	23	23	32	34	20	24
Date of delivery	21 11 1984	14.2.1985	24.3.1985	16 10 1985	1 12 1984	8.2.1985
Hospital	SGH	SGH	SHH	SGH	SHH	SHH
Presenting symptoms/signs						
Antecedent illness	Influenza-like illness	Sore throat, malaise	Diarrhoea, chest infection	Abdominal pain, shivering	Sore throat, malaise	None
Duration (h)	6	24	168	18	168	—
Temperature (°C)	37 5	37·8	38·3	36 8	36·6	38
Uterine contractions	Present	Present	Absent	Present	Present	Present
Clinical course	Induced abortion	Spontaneous abortion	Induced labour	Induced labour	Induced labour	Induced labour
Infant						
Gestation age (weeks)	20	27	32	30	38	40
Weight (g)	365	745	1280	1250	3340	3360
Outcome	Dead, abortion	Dead, abortion	Stillborn	Stillborn	Stillborn	Alive

SGH, St George's Hospital; SHH, St Helier's Hospital.

had been on the Isle of Wight. Following an uneventful antenatal course she presented in labour at 38 weeks gestation by dates. On clinical examination, the fetal heart rate was 50–60 beats/min, and the cervix was dilated to 4 cm. The membranes were intact. The membranes were ruptured artificially and thick meconium-stained amniotic fluid drained. Emergency lower segment caesarean section was performed immediately and a fresh stillborn but macroscopically normal male infant weighing 3340 g was born. The patient gave a history of a sore throat and viral-like illness for the week preceding admission. She was afebrile at the time of admission and postoperative progress was uneventful.

Patient 6.

A 24-year-old white European primigravida had an uneventful pregnancy from booking at 12 weeks gestation in August 1984 until February 1985 when she presented in labour at term by dates. The cervix was 4 cm dilated, the fetal heart rate was 160 beats/min and the membranes were intact. Her temperature was 38°C. The membranes were ruptured artificially and thick meconium-stained amniotic fluid drained. A scalp clip was attached. Progress to full dilatation of the cervix was rapid, but after a second stage of labour lasting 60 min, rotation of the baby and delivery by Keilland's forceps were required because of cardiotocograph signs of fetal distress. The Apgar scores were 5 at 1 min, 7 at 5 min and 9 at 10 min. Direct laryngoscopy of the infant did not show any meconium beyond the vocal cords. Initially the infant, a normal female, was kept with the mother but at 11 h of age she was noted to be grunting, cyanotic and tachypnoeic, with a temperature of 39°C. She was initially treated with 35% oxygen via a head box and empirically with penicillin and gentamicin. A full infection screen was performed at this stage. A diagnosis of listerial pneumonia and septicaemia was made 12 h later based upon isolation of the organism from swabs taken from the mother at the time of delivery and subsequently confirmed on blood cultures taken from the infant. Ampicillin was substituted for penicillin following results of sensitivity testing of the isolates. She was treated for 14 days and made a complete recovery. She was discharged home on the 16th day and, on follow-up, has maintained good progress.

In all patients the diagnosis of listerial infection was made after delivery of the fetus or newborn either on microbiological (patients 1, 4, 5 and 6) or histopathological findings (patients 2, 3, 4 and 5).

Laboratory findings

Microbiology

A summary of the findings is given in Table 2.

Endocervical swabs were taken in five women in labour and *Listeria monocytogenes* was isolated from three (patients 1, 5 and 6). Maternal blood, taken for culture in patients 1 and 3, grew *L. monocytogenes* in patient 1 only. Microbiological investigations were performed on the infants in patients 5 and 6. *L. monocytogenes*

Table 2. Microbiological findings in six patients with perinatal listeriosis

Cultures	Patient no.					
	1	2	3	4	5	6
Maternal						
Blood	+	ND	–	ND	ND	–
Endocervical swab	+	–	–	–	+	+
Infant						
Blood	ND	ND	ND	ND	ND	+
Cerebrospinal fluid	ND	ND	ND	ND	+	ND
Rectal swab	ND	ND	ND	ND	ND	+
Ear and nose swab	ND	ND	ND	ND	ND	+
Placenta	ND	ND	+	+	ND	ND
Serotype*	4b	–	4b	1a	4b	4b

+, *Listeria monocytogenes* isolated, –, *Listeria monocytogenes* not isolated; ND, not done.

* Serotyping performed by Central Public Health Laboratory, Colindale

was isolated from the cerebrospinal fluid of the stillborn infant in patient 5, and from the swabs from the ear, nose and rectum of the infant in patient 6. Neonatal blood cultures, subsequently done because of evidence of sepsis in the latter case, also grew *L. monocytogenes*. Segments of placenta were sent for culture in two patients (patients 3 and 4) and *L. monocytogenes* was isolated from both.

The isolates of the *L. monocytogenes* were serotyped by the Central Public Health Laboratory at Colindale; those from patients 1, 3, 5 and 6 were of serotype 4b and that from patient 4 serotype 1a.

Histopathology

A summary of the findings is given in Table 3.

The four patients with intrauterine deaths displayed the disseminated granulomata/abscesses characteristic of the disease. These were seen macroscopically as pinhead nodules in patient 3. Gram-positive bacilli were demonstrable within these lesions histologically. Gross and microscopic examination failed to reveal any other cause for the fetal death.

In contrast, in the fresh stillbirth (patient 5), the relevant findings were restricted to the central nervous system. There was bulging of hyperaemic meninges with excess cerebrospinal fluid. Abundant exudate was seen around the base of the brain and in the sylvian fissures. The aqueduct of Sylvius was compressed and the foramina of Luschka and Magendie were occluded by exudate although the fourth ventricle was not dilated. Gram-positive bacilli were demonstrable in the exudate on histology. There were stigmata of anoxia with petechial haemorrhages over several visceral surfaces.

Placentas were available for examination in five patients (nos 1, 2, 3, 4 and 5). All showed macroabscesses up to 10 mm in diameter and focal villitis histologically. Funisitis was seen in one patient (no. 5) and chorioamnionitis was seen invariably; Gram-positive bacilli were demonstrated in all patients histologically.

Discussion

Although *Listeria monocytogenes* is widespread in nature and the carrier rate in normal human population approximates to 5%, perinatal listeriosis appears to be more prevalent in the north of France with occasional reports of outbreaks in other parts of the world (Editorial 1980; Barza 1985). In our patients foreign travel could not be implicated and although one of the women initially booked outside the districts in the Isle of Wight, her subsequent antenatal progress was uneventful. Although most cases are sporadic, outbreaks have been associated with contaminated coleslaw, raw and pasteurized milk and goats' cheese (Schlech *et al.* 1983; Fleming *et al.* 1985). The localized outbreak probably represents a clustering of sporadic cases in our two districts, but detailed epidemiological studies were not performed.

Two groups of patients are commonly affected by listeriosis, the immunocompromised and the pregnant. During pregnancy, characteristically, the women may present with two or more febrile episodes or may be afebrile with an influenza-

Table 3. Histopathological findings in six patients with perinatal listeriosis

	Patient no.					
	1	2	3	4	5	6
Placenta						
Weight (g)	170	225	370	350	600	610
Histology						
Funisitis	−	−	−	−	+	NR
Chorioamnionitis	+	+	+	+	+	NR
Villitis	+	+	+	+	+	NR
Macro and microabscesses	+	+	+	+	+	NR
Decidual necrosis	+	−	−	+	−	NR
Infant						
Visceral abscesses	+	+	+	+	−	Alive
Meningitis	−	−	−	Not examined	+	

NR, Not received for pathological examination; +, present; −, not present like illness. This was observed in all our patients. Untreated maternal infection invariably results in fetal damage in the form of abortion, stillbirth or neonatal sepsis (Relier 1979). Neonatal listeriosis may present either early or late (Larsson *et al.* 1978). The early type presents within 2 days of birth with signs of septicaemia and results from intrauterine infection. The late form of disease appears after the fifth day of life, usually presenting as meningitis and results from infection during or soon after delivery. All our patients conformed to this recognized clinical pattern with the exception of the fresh stillborn infant where meningitis *in utero* was seen instead of the expected generalized septicaemia.

As in all patients with perinatal infection, early diagnosis requires close liaison between clinician and microbiologist. A rapid method for diagnosis utilizes the propensity of *L. monocytogenes* to colonize amniotic epithelium; smears prepared from scraping the amniotic epithelial cells of the placenta are examined for the characteristic Gram-positive bacilli (Nessmann-Emanuelli *et al.* 1983). Early diagnosis and treatment can modify the poor prognosis of the infection (Robertson *et al.* 1979; Relier 1979; Fleming *et al.* 1985) and early treatment may have been instrumental in salvaging one infant in our series although the antibiotic of choice, ampicillin (Editorial 1985), was not given initially. Despite other reports (Relier 1979; Robertson *et al.* 1979) an early diagnosis would not have altered the outcome in our five patients who presented with intrauterine deaths. The prodromal febrile episodes or 'viral-like' illness are not specific to listeriosis and, furthermore, may precede the expulsion of a macerated fetus by only a matter of hours.

The pathological findings of perinatal listeriosis are well documented (Benirschke & Driscoll 1974; Larroche 1977; Fox 1978). Postmortem examination, including histological assessment of macerated organs, proved to be helpful and prompted the diagnosis of listerial infection as a cause of fetal death in four of our patients. Although these cases were probably sporadic, the possibility of an outbreak on a larger scale must be borne in mind.

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Ketoacidosis in pregnancy: an unusual presentation of diabetes mellitus. Case reports

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Case reports

Patient 1

A previously fit 29-year-old white European gravida 2, para 0, presented at 29 weeks gestation with a 3-day history of nausea, vomiting, polyuria and polydipsia. Since she had had a 16-week incomplete abortion 44 weeks before booking followed by secondary amenorrhoea, the expected date of delivery of her current pregnancy was uncertain. On booking examination there were no abnormal findings and in particular she was normotensive and at her ideal body weight. Ultrasound scan showed a normal fetus whose biparietal diameter and abdominal girth measurements were consistent with 25·5 weeks gestation. Although initial urinalysis with Ames multistix had shown 0·25% glycosuria, subsequent testing by her general practitioner and in the antenatal clinic was negative. There was neither a past nor family history of insulin-dependent diabetes or risk factors for developing gestational diabetes.

On admission she was orientated, apyrexial but dehydrated and ketotic with Kussmaul respiration. Her pulse was 100 beats/min and her supine blood pressure 120/80 mmHg. There were no signs of diabetic retinopathy or neuropathy. Doppler ultrasound confirmed the presence of a fetal heart. The results of biochemical investigations are shown in Table 1.

Routine therapy for diabetic ketoacidosis was commenced using intravenous normal saline, potassium supplements and insulin administered through a continuous infusion pump. Subsequently she was treated with Actrapid insulin thrice daily with Monotard insulin at night and her daily insulin requirement of 52 i.u. rose to 75 i.u. as the pregnancy proceeded. Further serial fetal ultrasound scans showed growth on the 50th centile and regular cardiotocographs were normal. Labour was induced at 38 weeks and as the cervix was unfavourable induction was facilitated by two vaginal prostaglandin tablets 3 mg (Upjohn, UK). The ensuing labour, which was continuously monitored, proceeded rapidly and 6 h later she gave birth to a healthy female infant of 3·45 kg. There was no problem with neonatal hypoglycaemia or other complications referrable to maternal diabetes mellitus. No insulin was required in the puerperium but subsequent blood glucose levels confirmed persisting diabetes mellitus which, at 3 months, required treatment with insulin at a daily dose of 30 i.u.

Patient 2

A 31-year-old white European woman, gravida 4, para 1, was admitted at 29 weeks gestation with diabetic ketoacidosis. Eight years previously a right tubal pregnancy had resulted in a salpingectomy and 6 years later following an intervening incomplete abortion, she was delivered of a 2·8 kg male infant at 38 weeks gestation. In the current pregnancy, booking examination at 13 weeks was normal and showed her to be normotensive and at her ideal body weight. There was no past nor family history of insulin-dependent diabetes or risk factors for developing gestational diabetes. Subsequent routine urinalysis at antenatal checks had not revealed glycosuria. On admission she was hyperventilating and ketotic but not dehydrated, with a pulse of 70 beats/min and a supine brachial blood pressure of 105/60 mmHg. Physi-

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Table 1. Biochemical findings in two patients on admission

	Patient 1	Patient 2	Normal range for pregnancy
Plasma glucose (mmol/l)	19·5	29·5	<6
Plasma Na^+ (mmol/l)	125·0	129·0	130–142
Plasma K^+ (mmol/l)	4·6	3·9	3·15–4·65
Plasma HCO_3 (mmol/l)	6·0	11·1	23·2–24·6
Plasma urea (mmol/l)	6·2	4·5	3·3 mmol/l
Blood H^+ (mmol/l)	71·0	50·0	36–44
Base excess	−23·0	−12·4	−2·2–−4·6
*P*a co_2 (kPA)	1·5	2·93	4·0–5·3
*P*a o_2 (kPA)	16·9	15·1	9·3–12
Urine ketones	+++	+++	Negative
Plasma ketones	+++	+++	Negative
Hb A1. (% total Hb)	8·0	8·0	5·5–8·5
Islet cell antibodies	Not done	Positive	Negative

cal examination was otherwise normal and the fetal heart sounds were present. The results of biochemical investigations on admission are shown in Table 1. Routine treatment with intravenous normal saline, potassium and insulin corrected the metabolic abnormalities and satisfactory diabetic control was rapidly established with an appropriate diet and daily subcutaneous insulin dose of 103 units which subsequently fell to 60 units. Ultrasound scan showed a normal fetus with abdominal girth well above the 90th centile and biparietal diameter just below the 50th centile. The abdominal girth returned to the 50th centile as the pregnancy progressed. At 37 weeks, because of falling material weight and decreased fetal movements, labour was induced with prostaglandin E_2 tablets (Upjohn, UK) and accelerated by artificial rupture of membranes and oxytocin infusion. After 3 h of labour she was delivered of a 3·19 kg male. At birth the infant was noted to be dusky and examination revealed a cardiac defect, later diagnosed as transposition of the great vessels and treated by septostomy. There were no neonatal complications attributable to maternal diabetes mellitus.

In the puerperium, maternal blood glucose concentrations were all 6 mmol/l and a 75 g glucose tolerance test at 6 weeks postpartum showed a fasting blood sugar of 4·8 mmol/l and a 2-h value of 6·9 mmol/l. However, the value at 30 min was elevated at 11·2 mmol/l. The patient's serum was positive for complement fixing islet cell antibodies.

Discussion

When diabetes mellitus is first seen during pregnancy the diagnosis is usually either previously undiagnosed non-insulin-dependent (Type 2) diabetes mellitus, or gestational diabetes in which the glucose-tolerance test returns to normal after delivery. In these conditions although insulin secretion is inadequate to maintain euglycaemia it is usually sufficient to prevent ketoacidosis (Hollingsworth 1984).

As the more severe beta cell deficiency of insulin-dependent (Type 1) diabetes mellitus develops over several months or even longer (Srikantha *et al.* 1983; Gorsuch *et al.* 1981), occasionally such patients might be expected to present with diabetic ketoacidosis, particularly during the third trimester of pregnancy when developing insulin deficiency would be compounded by the insulin resistance of late pregnancy (Kuhl *et al.* 1985). Although ketoacidosis in the known insulin-dependent patient is well recognized, the only previously reported case arising *de novo* during pregnancy was a 32-year-old multiparous Jamaican who presented at 21 weeks gestation with hyperglycaemia and ketoacidosis following 2 weeks of vomiting (Livesley & Neary 1968). In this case, although the blood glucose values were only reported 1 month postpartum, there was no suggestion of subsequent insulin dependence. Also, she had previously given birth to a baby weighing 5 kg and it seems likely that prolonged vomiting in a patient with a non-insulin dependent diabetes mellitus resulted in hyperglycaemia and severe starvation ketosis, a condition to which the pregnant woman is particularly prone (Metzgar *et al.* 1982). The contention by Livesley & Neary (1968) that the primary diagnosis was lactic acidosis seems unlikely in the clinical setting and was not supported by the plasma lactate concentrations.

In contrast, our first patient required insulin therapy within 3 months of delivery and is clearly insulin-dependent. While the type of diabetes remains to be established in our second patient, hyperglycaemia following a glucose load and positive complement fixing islet cell antibodies are, in context, suggestive of developing insulin-dependent diabetes mellitus (Irvine *et al.* 1980).

In view of the high perinatal mortality of up to 90% reported in diabetic ketoacidosis of pregnancy (Kitzmiller 1982; Brumfield & Huddleston 1984), the successful delivery of live infants without complications attributable to maternal diabetes in our two patients is noteworthy. The extent to which ketoacids *per se* are toxic to the fetus is controversial but the findings in our patients and in the one described by Livesley & Neary (1968) suggest that the fetus, which is able to utilize ketone bodies (Robinson & Williamson 1980), may not be adversely affected by a single episode of ketoacidosis. Thus, fetal morbidity and mortality in diabetic ketoacidosis may be more influenced by previously poor diabetic control (Karlsson & Kjeller 1972) and the reduction in feto-placental blood flow caused by maternal hypovolaemia (Arias 1975). This is consistent with the findings in our patients in whom the haemoglobin A1 was normal and marked intravascular hypovolaemia, as estimated from the plasma urea concentration, was not present.

As diabetic ketoacidosis could result in fetal and maternal mortality, earlier diagnosis of hyperglycaemia would clearly be valuable. The advantages of routine screening at 28–32 weeks are proven for detecting gestational diabetes (Lind & Anderson 1984) and it is of interest that our patients and the one reported by Livesley & Neary (1968) would have been diagnosed and episodes of ketoacidosis prevented by 28-week screening.

Finally, as it is probable that patients with sufficient insulin deficiency to develop diabetic ketoacidosis during pregnancy will subsequently develop insulin-dependent diabetes mellitus and as other autoimmune diseases are known to deteriorate in the postpartum period (Walfish & Chan 1985) such patients should be followed-up even though their routine postpartum glucose tolerance testing may be normal. Intermittent testing for glycosuria and estimation of haemoglobin A1 will facilitate the early detection of deteriorating glucose tolerance and avoid a prolonged period of potentially harmful asymptomatic hyperglycaemia.

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Advanced unruptured interstitial gestation. Case report

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Case report

A 26-year-old African woman was first seen in the antenatal clinic when she had had 42 weeks amenorrhoea in her third pregnancy. Ten years earlier she had had a spontaneous vertex delivery of a live male infant at term, with birthweight of 2·4 kg. This child had died at 18 months of age. Seven years earlier she had had an emergency caesarean section, indication unknown, and given birth to a 2·0 kg male infant which died in the neonatal period. In her present pregnancy she had spent many weeks in a local mental hospital suffering from schizophrenia. At her first antenatal attendance the uterus was estimated to be equivalent to a 30 week gestation and the fetal heart was clearly heard. It was assumed that her dates were incorrect (ultrasound scanning was not available). She was reviewed at weekly intervals but after 2 weeks the uterus was noted to be tense and the fetal heart was absent. A plain abdominal X-ray showed a fetus which was 'small-for-gestational age, hyperflexed, Spalding's sign present'. Coagulation studies were normal, but attempts to induce labour with intravenous oxytocin and later intravenous prostaglandin E_2 failed to promote any detectable uterine activity. Extra-uterine pregnancy was considered and hysterosalpingography revealed an empty uterine cavity, apparently confirming this diagnosis.

Laparotomy was therefore undertaken which showed a large cystic swelling of the left uterine cornua, about 20 cm in diameter, lying above the origin of the left round ligament but with the tube and ovary drawn up onto its superior surface. The left infundibulo-pelvic ligament was elongated. Bonney's myomectomy clamp was applied to the uterus and a left cornual resection with left salpingo-oophorectomy was performed. The uterus was repaired in three layers with catgut. Her postoperative recovery was uncomplicated.

The cut surgical specimen is shown in Fig. 1, and explained in the accompanying drawing. The fetus was female, weighed 2·0 kg, and despite advanced maceration there were no apparent congenital malformations.

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Discussion

Interstitial gestation is a rarity amongst ectopic pregnancies, occurring in 1·1–6·8% of collected series (Felmus & Pedowitz 1953). There is a suggestion that it is proportionately rarer where ectopic gestation is common, and this is supported by an unpublished series of 1000 consecutive ectopic pregnancies presenting at the Kenyatta National Hospital in which only seven were interstitial (S. R. Patel, personal communication). It should be differentiated from angular pregnancy which has cornual implantation of the placenta with growth of the gestational sac into the normal uterine cavity; cornual pregnancy which is a term usually reserved for gestation in one horn of a bicornuate uterus; and pregnancy in a rudimentary horn.

There is a feeling that interstitial pregnancy ruptures later than gestation in the more distal portions of the tube (Moir & Myerscough 1971). In one series 10 of 45 ruptured after 12 completed weeks of amenorrhoea (Felmus & Pedowitz 1953). Rupture is usually extensive and haemorrhagic and emergency hysterectomy has often been required.

Advanced unruptured interstitial gestation has been described but it is extremely rare. A case was reported without details by Gustafson (1953) and a case similar in some features to this one was described by Stapleton (1935). An unruptured interstitial gestation diagnosed at 5

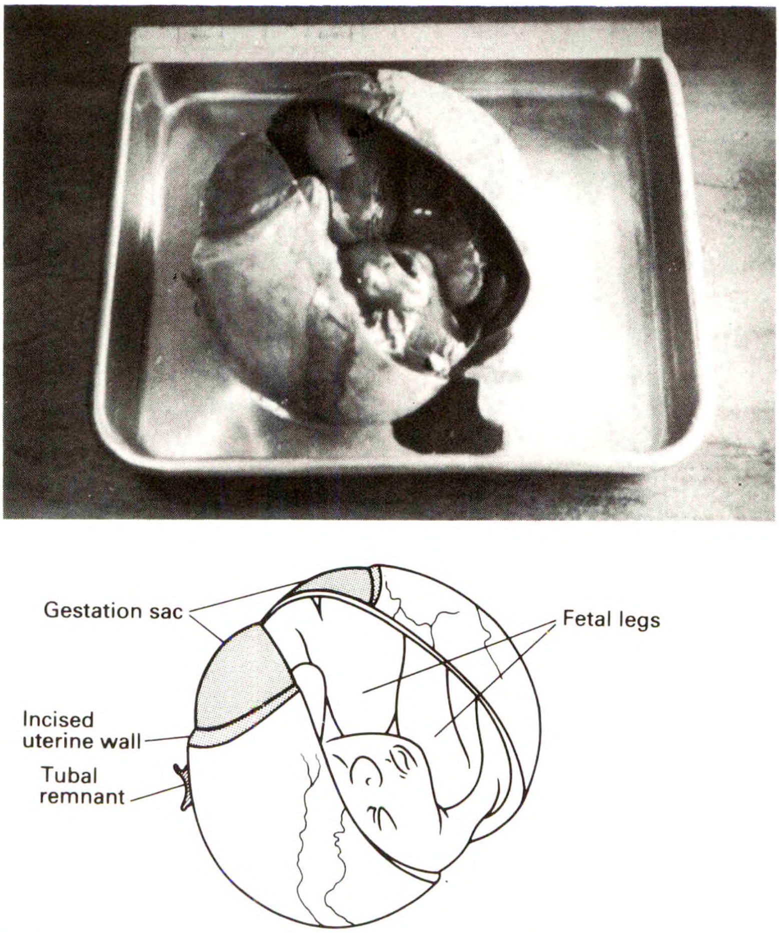

Fig. 1. Opened operative specimen (ruler is 30 cm long) with diagrammatic explanation.

months gestation is beautifully illustrated by Falls & Holt (1961).

In our patient a diagnosis might have been made in time to save the fetus if more respect had been paid to the patient's dates, which were almost certainly correct. The availability of diagnostic ultrasonography might also have offered an opportunity for fetal salvage.

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Intussusception in pregnancy. Case report and review of the literature

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Case report

A 23-year-old woman was admitted to the obstetric ward at 37 weeks in her fourth pregnancy. She complained of colicky generalized abdominal pain and nausea for 6 h before her admission. The antenatal period had been uneventful. On examination the uterus was not tender, consistent with 37 weeks gestation, and a fetal heart beat was present. There was tenderness on palpation in the epigastrium and right hypochondrium, but there was no abdominal guarding and normal bowel sounds were present. Her pain settled but returned 48 h later with vomiting of bile-stained fluid. Biliary colic was diagnosed. A full blood count, plasma electrolytes and serum amylase were normal and a plain abdominal X-ray showed no abnormality. She was treated with intravenous fluids and again her symptoms quickly settled. Four days after admission an ultrasound examination was performed. This showed a normal gall bladder, liver and kidneys but also revealed an elliptical cystic mass extending from the renal angle into the right iliac fossa. The nature of the mass was uncertain but it was considered that it might be dilated loops of small bowel. The patient remained asymptomatic. A week after admission she developed a further recurrence of right sided upper abdominal pain and vomiting. At the time she also reported reduced fetal movements. Cardiototography showed diminished baseline variability and reduced fetal movements. Because of the abnormal fetal heart trace, labour was induced and 1 h later, at only 3 cm cervical dilatation, the fetal heart tracing began to show late decelerations. In view of the fetal heart recording and the continuing unexplained abdominal pain it was decided to perform a caesarean section together with exploratory laparotomy. The abdomen was opened through a right paramedian incision and a live female infant was born by lower segment section. Abdominal exploration revealed an ileo-ilial intussusception impacted in the caecum. It was impossible to reduce the intussusception and therefore a right hemicolectomy and ileal resection was performed, continuity being restored with an end to end ileo-colic anastamosis. Examination of the resected bowel showed 30 cm of necrotic ileum within the caecum, but no cause for the intussusception could be found. Both mother and child made an uneventful postoperative recovery and were discharged home 14 days after the birth.

Discussion

Intestinal obstruction is an uncommon complication of pregnancy although one which has been reported with increasing frequency. Morris (1965) reported a rate of 1 in 13 687 deliveries before 1950 and a rate of 1 in 3163 deliveries after 1950. Intussusception is said to account for between 4 and 6% of intestinal obstruction in pregnant women (Goldthorp 1966; Beck 1974). Despite this only 14 patients with intussusception in pregnancy, excluding the present one, have been reported in the literature during the past 30 years (Table 1).

Intussusception during pregnancy has been recognized as one of the most dangerous forms of bowel obstruction (Svesko & Pisani 1960). Chaffin *et al.* (1937) described their own case and reviewed the literature. They found 20 reported cases of intussusception in pregnancy or the puerperium during the years 1870 to 1936. In their series the maternal mortality was 75% and in those cases occurring before delivery only

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Table 1. Reported cases of intussusception complicating pregnancy or the puerperium: 1953–1979

Authors	Gestation (weeks)	Type of intussusception	Precipitating cause	Outcome	
				Maternal	Fetal
Moore *et al.* 1967	16	Ileo-caecal	Chronic inflammation of terminal ileum	Recovered	Preterm, survived
Morris 1965	18	Ileo-ileal	Meckel's diverticulum	Recovered	Full-term, survived
Aston & Machleder 1975	19	Ileo-transverse colon	Cavernous haemangioma of distal ileum	Recovered	Full-term, survived
Labayle *et al.* 1976	20	Intussusception of free end of jejunum following previous small bowel bypass for obesity		Recovered	Spontaneous abortion
Bourque & Gibbons 1979	24	Ileo-ileocolic	Idiopathic	Recovered	Preterm, neonatal death
Svesko & Pisani 1960	29	Ileo-ileal	Meckel's diverticulum	Died	Preterm, stillbirth
Bruhlmann *et al.* 1980	30	Jejuno-jejunal	Idiopathic	Recovered	Preterm, stillbirth
Bourque & Gibbons 1979	35	Jejuno-jejunal	Idiopathic	Recovered	Preterm, survived
Arriaga Martinez 1966	35	Ileo-ileal	Congenital redoublication of internal mucosa of the terminal ileum	Recovered	Preterm, survived
Baker *et al.* 1953	36	Ileo-caecal	Pedunculated polyp at apex of intussusception	Recovered	Preterm, survived
Gay *et al.* 1953	Puerperium	Ileo-caecal	Meckel's diverticulum	Recovered	Full-term, survived
Gibbins & Symmers 1953	Puerperium	Ileo-caecal	Meckel's diverticulum	Recovered	Twin I. Preterm, survived Twin II. Preterm, stillbirth
Burmeister 1962	Puerperium	Ileo-caecal	Mucocele of appendix	Recovered	Full-term, survived
Henscher & Imig 1976	Puerperium	Retrograde jejunogastric intussusception following previous gastro-jejunostomy		Recovered	Full-term, survived

28% of the infants survived. Most of these cases were before current diagnostic and therapeutic facilities were available. During the past 30 years there has been considerable improvement in both maternal and fetal survival in reported cases with only one maternal death and a fetal survival of 60% in those cases occurring before delivery. In the puerperium maternal ileus has no direct bearing upon fetal survival.

Intussusception accounts for approximately 80–90% of intestinal obstructions in infants. In contrast intussusception in adults is a rare condition which produces approximately 5% of mechanical intestinal obstruction (Ponka 1967). Whereas the aetiology of intussusception is idiopathic in over 90% of affected infants (Strang 1959), a demonstrable cause, according to most authors, is found in most affected adults (Donhauser & Kelly 1950; Weilbaecher *et al.* 1971). Of the 14 reported cases of intussusception occurring in pregnancy or the puerperium during the past 30 years, a precipitating cause was found in 11 (79%), with ileo-caecal intussusception the most common type and Meckel's diverticulum the most common precipitating factor. Although bowel neoplasms are an important underlying feature in the majority of adult intussusceptions (Sanders *et al.* 1958; Weilbaecher *et al.* 1971), because of the relatively young age of pregnant patients, neoplasia was not an important factor and one fifth of all cases were of the idiopathic childhood type.

Intussusception in infants is characterized by the sudden onset of severe cramping abdominal pain, vomiting and eventually the passage of blood and mucus *per rectum*. An intestinal or rectal mass is usually palpable on examination and X-ray studies with barium are a most useful diagnostic aid and in selected patients are of therapeutic value (Ponka 1967). However, the clinical picture and X-ray findings associated with intussusception in adults are bizarre and a correct pre-operative diagnosis is rarely made (Cotlar & Cohn 1961). The chief complaint in adults is of abdominal pain which is usually colicky in nature (Weilbaecher *et al.* 1971), although in 25% there is no pain (Deiterling *et al.* 1953). Vomiting is usually mild (Cotlar & Cohn 1961) and rectal bleeding is infrequent (Stubenbord & Thorbjarnarson 1969). Abdominal tenderness is present in almost all patients but a palpable mass is found in only one quarter (Stubenbord & Thorbjarnarson 1969) and abnormal bowel sounds are present in only one third (Cotlar & Cohn 1961). Plain abdominal X-rays are only occasionally helpful in diagnosis (Foulds & Beamish 1970) and the findings with barium contrast studies are often misleading or unspecific (Bruhlmann *et al.* 1980), achieving a definitive diagnosis in only 12–35% (Stubenborn & Thorbjarnarson 1969; Nagorney *et al.* 1981).

Intussusception occurring in pregnancy is a potentially fatal complication because of the difficulty and delay in diagnosis and the reluctance to operate on pregnant women. Of the 14 cases occurring in pregnancy or the early puerperium reported during the last 30 years, the principal symptoms have been colicky upper abdominal pain, vomiting and constipation. However pain, vomiting and constipation occur sufficiently often with otherwise normal pregnancy to delay recognition of mechanical obstruction (Morris 1965). Rectal bleeding occurred in only five of the 14 pregnancies and findings on physical examination were atypical. Some degree of upper abdominal tenderness was recorded in almost all patients but a palpable mass, other than the uterus, was felt in only two and decreased bowel sounds reported in only four. Routine laboratory studies are of little value, pregnancy being associated with a leukocytosis (Mitchell *et al.* 1966). Plain abdominal X-rays were useful in demonstrating gaseous distension of the bowel in five cases and in one case the correct pre-operative diagnosis was made on plain abdominal X-ray after delivery (Bruhlmann *et al.* 1980). However, in the majority of cases plain abdominal X-ray showed no abnormality. Barium studies, while of value in the non-pregnant (Nagorney *et al.* 1980) and in the puerperium (Burmeister 1962), are impracticable antenatally because of the radiation risk to the fetus. The difficulty in diagnosis is emphasized by the fact that in only three of the 14 cases was the correct pre-operative diagnosis achieved, all in the puerperium and all by X-ray (Burmeister 1962; Henscher & Imig 1976; Bruhlman *et al.* 1980). In all other cases the correct diagnosis was only established at laparotomy or post-mortem, the commonest indication for laparotomy being intestinal obstruction.

Diagnosis in this case was made at laparotomy 7 days after the onset of symptoms. Almost all authors have stressed the delay from initial presentation to final diagnosis which varied from 2 days (Baker *et al.* 1953) to 15 weeks (Bourque & Gibbons 1979). Considering the difficulty in clinical diagnosis and the limited role of X-rays, ultrasound would appear to offer the best hope of early diagnosis. The diagnosis of intussusception by ultrasound, describing 'single or double concentric rings of sonolucency surrounded by a course central echogenic focus' has been reported (Uhland & Parshley 1978; Morin *et al.* 1981). In our patient, and also the one reported by Bourque & Gibbons (1979), ultrasound provided an early clue to the correct diagnosis but in both the findings were misinterpreted with resultant delay in treatment.

In this case delay in diagnosis resulted in infarction of the ileum within the intussusception and resection of the terminal ileum with its specialized absorptive surface. Subsequently the patient has had increased bowel frequency due to reduced absorption of bile salts and has required long term antidiarrhoea medication and vitamin B_{12} supplements.

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Conservative management of spontaneous rupture of the liver in pregnancy. Case report

DAVID R. WOODHOUSE

Case report

The patient was a 22-year-old woman in her fourth pregnancy who presented at 36 weeks gestation with a 24-h history of epigastric and right upper quadrant pain radiating to her back.

Her antenatal care had been uncomplicated and specifically there had been no evidence of pre-eclampsia. Serology was negative and the patient had not travelled overseas.

Four years previously she had given birth to twins after an uncomplicated pregnancy. Her next child had died of sudden infant death syndrome at 10 weeks, while a third pregnancy had ended in a first trimester abortion. There was no relevant past or family history and in particular no liver disease. She was taking no medications and smoked 10 cigarettes/day.

On examination she was afebrile, normotensive with a pulse rate of 80/min. Her chest was clinically clear and abdominal examination revealed mild epigastric tenderness without hepatomegaly. Bowel sounds were normal and there was no evidence of gastrointestinal obstruction.

The uterine fundus was consistent with dates, non-tender and without palpable contractions or evidence of placental separation. The fetal heart rate was 140/min, the cervix 1 cm dilated with the fetal head high in the midcavity.

Shortly after admission the patient vomited 500 ml of undigested food followed later by 200 ml of bile-stained fluid. She was given intravenous fluids, analgesia and antiemetics.

An abdominal ultrasound and cholecystosonogram, using a 3·5 MHz transducer, performed on the following day showed no visible pathology of the liver, gall bladder, biliary tree, right kidney or pancreatic region.

Labour commenced spontaneously 48 h after admission and was augmented by amniotomy and oxytocin infusion. Normal vaginal delivery of a liveborn girl followed a 12-h labour with a blood loss of 70 ml. During labour the patient's blood pressure rose to 140/90 mmHg on one occasion; there was no proteinuria. After delivery her abdominal pain was unchanged. She remained afebrile but developed a mild tachycardia up to 100/min. The pain was now radiating to the right loin and right iliac fossa. The liver was not clinically enlarged.

Chest X-ray showed dense consolidation at the right base in keeping with inflammatory changes in that area, while abdominal X-rays revealed a prominent liver shadow but no other abnormalities.

The day after delivery haematological studies showed a haemoglobin level of 8·4 g/dl (11·3 g/dl pre-admission), white blood cells 18 900/ml, platelets 337 000/ml and an ESR 55 mm/h.

Blood gases, sputum and blood cultures were negative and liver function studies were normal except for an alkaline phosphatase 195 u/l (normal 30–100) and gamma glucuronyl transferase 75 u/l (normal 6–46).

A biliary scan (Technetium biliary scintography) was performed. In the early images the liver was outlined revealing a 7 × 15 cm defect in the lateral aspect of the right lobe suggesting a space occupying lesion.

A computerized tomogram scan (Fig. 1) delineated the lesion more precisely, showing a fresh haematoma present in the mid-portion of the right lobe of the liver tracking via a laceration to the subcapsular space. At that site there was a large subcapsular haematoma displacing the liver medially.

As there were no signs of continuing or intraperitoneal bleeding it was decided to manage the patient conservatively and she was transfused. The liver was now palpable below the costal margin and the pleural effusion clinically evident. During the post-partum period the patient's blood pressure was 140/90 mmHg on

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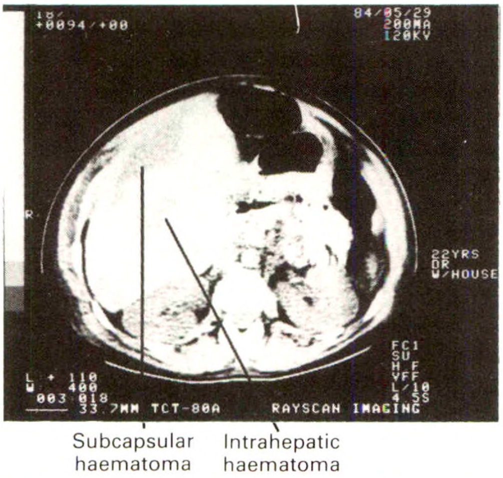

Fig. 1. CT scan showing extensive haematoma in the right lobe of the liver.

several occasions with mild dependent oedema but no proteinuria.

Lactation was suppressed with bromocriptine and over the subsequent week there was gradual resolution of her pain and of the pleural effusion. After transfusion her Hb was 11·2 g/dl. There was a thrombocytosis up to 843 000/ml and coagulation studies showed a prothrombin index of 98% with a thrombin clotting time 11 s (10–13) and an activated partial thrombin time 29 s (22–29).

Follow-up ultrasonography and liver spleen scans showed no increase in haematoma size. The liver remained 3 cm palpable below the costal margin.

With continued improvement she was discharged, 3 weeks after admission, with a normal white blood cell count and a haemoglobin of 12·3 g/dl.

One month post-partum, a liver scan showed no decrease in haematoma size but the lesion was now solid with fibrosis. At 6 weeks post-partum the liver remained palpable but non-tender. The patient was well, normotensive and the pelvis had returned to normal. Intercourse had resumed and an IUCD was inserted for contraception.

Discussion

Over 120 cases of spontaneous rupture of the liver have been reported since Abercrombie (1844) first described the syndrome. In the non-pregnant patient, hepatic rupture is almost always due to trauma, resulting in often fatal haemorrhage. In the so-called spontaneous hepatic rupture of pregnancy the causes remain unclear though the results may be equally tragic with mortality rates up to 59% (Bis & Waxman 1976).

The most common condition associated with hepatic rupture in pregnancy is pre-eclampsia, and less commonly hepatic neoplasms including haemangiomas, syphilis, malaria and vascular abnormalities including aneurysms.

Utley (1971) noted that 58% of patients with hepatic rupture had pre-eclampsia and 16% eclampsia; but it is noteworthy that although pre-eclampsia is commoner in primigravidae, hepatic rupture occurs far more frequently in multigravid patients in the ratio 10:1 (Asiz *et al.* 1983).

The role that even minor trauma plays in starting bleeding in areas of haemorrhagic necrosis in a pre-eclampsia affected liver is unknown. The pre-eclamptic syndrome is a clinical diagnosis with well-known diversity in severity and speed of onset of its components. The correlation of changes at the cellular level with the severity of the clinical picture can only be assumed in the absence of liver biopsy and it may be that in some patients, severe cellular alterations may occur in the parenchyma of numerous organs before the clinical picture is regarded as serious. Trauma, so minor as to be ignored by the patient, or even the trauma of parturition, vomiting or convulsions may be enough to start haemorrhage.

The statement is repeatedly made (Bis & Waxman 1976; Baumwol & Park 1976; Herbert & Brenner 1982) that patients with spontaneous rupture of the liver in pregnancy do not survive without surgery, though Hibberd (1976) reported one patient who survived without surgery in whom intrahepatic haemorrhage was controlled by a gravity suit.

Henney *et al.* (1983) describe the entity of spontaneous hepatic rupture as a biphasic syndrome. In phase I there is intrahepatic or subcapsular haematoma formation without rupture of the capsule. Once the capsule is ruptured the syndrome enters phase II with life threatening haemorrhage and surgery is required.

In pregnancy, Henney *et al.* (1983) suggest that conservative management would be justified if there was no evidence of capsular rupture, but that caesarean section should be undertaken to prevent rupture of the haematoma by the 'endogenous trauma of parturition'.

In the present patient the primary lesion would appear to have been an intrahepatic haematoma in the right lobe tracking to the subcapsular region. In retrospect, bleeding into the liver started at least 72 h before labour began. The trauma of parturition may have caused further bleeding with extension to the subcapsular region at which stage the usual late diagnosis was made. As the patient remained in phase I and had been delivered, conservative management appeared justified.

Conclusion

Spontaneous rupture of the liver is an uncommon but potentially fatal complication of pregnancy generally associated with pre-eclampsia and having a mortality in excess of 50%. The present case describes conservative management in a patient with an unruptured haematoma.

It is suggested that with the availability of modern technology to diagnose and stage the syndrome, conservative management is justified in the post-partum patient where pre-eclampsia in controlled or absent.

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Unilateral polycystic ovary. Case report

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Case reports

Patient no. 1

A 20-year-old unmarried nulliparous woman presented to the gynaecology clinic in February 1983 with a history of intermittent right iliac fossa pain of 9 months duration. The episodes of sharp pain were associated with nausea and vomiting, and there was severe deep dyspareunia. She had been taking the combined contraceptive pill for 1 year, before which her menstrual cycle had been regular. There was no relevant past history and on examination she appeared well, with no abnormality on abdominal or pelvic examination. She was admitted the following month for a diagnostic laparoscopy, and examination under anaesthesia suggested the right ovary to be firm and slightly enlarged. Laparoscopy confirmed that the right ovary was 4–5 cm in diameter with a smooth featureless capsule. The left ovary and remainder of the pelvis, including the appendix, appeared normal.

Because the nature of the ovarian enlargement was uncertain, and in view of the fact that her symptoms could be explained by repeated torsion, an oophorectomy was recommended. She accepted this advice and the following week a right oophorectomy was performed, and a biopsy taken from the left ovary. Prolene was used to repair the right adnexum and the left ovary. She made an uneventful recovery and was discharged home after 6 days. On review in the clinic at 6 weeks and at 6 months she remained pain free.

Histology was expected to confirm a fibroma or teratoma. Surprisingly, microscopy revealed a thickened cortex extending into the medulla, multiple follicular cysts up to 10 mm in diameter and partially-luteinized theca cells (Fig. 1). Despite the absence of theca cell hyperplasia, the ovary therefore had the characteristic appearance of a polycystic ovary, typical of the Stein–Leventhal syndrome. The section from the left ovary contained numerous primordial follicles in normal cortex (Fig. 2).

An ultrasound scan after the operation confirmed a normal left ovary. On stopping the contraceptive pill, spontaneous ovulation occurred with regular menstruation and normal mid-luteal progesterone levels. She has recently conceived.

Patient no. 2

A 20-year-old married woman first presented to the gynaecology clinic in April 1982 with right iliac fossa pain for 48 h. The sharp pain was associated with vomiting but no other gastro-intestinal symptoms. She had a 6-month history of secondary amenorrhoea, after stopping the combined contraceptive pill. She had no symptoms of pregnancy and a recent pregnancy test had been negative. Before taking oral contraceptives her menstrual cycle had been erratic with heavy periods every 6–10 weeks. There was no other relevant history and the only specific finding on examination was some deep tenderness in the right iliac fossa. Pelvic examination was normal.

She had a normal ESR and white cell count and a repeated pregnancy test was negative. Conservative management was adopted and the pain settled within 48 h.

Her secondary amenorrhoea persisted and she was reviewed in the clinic 2 months later. Serum prolactin and thyroxine levels were normal but there was a raised serum luteinizing hormone (LH) (25·9 i.u./l) and low follicle stimulating hormone (FSH) level (1·5 i.u./l). The serum testosterone was raised (3·6 nmol/l).

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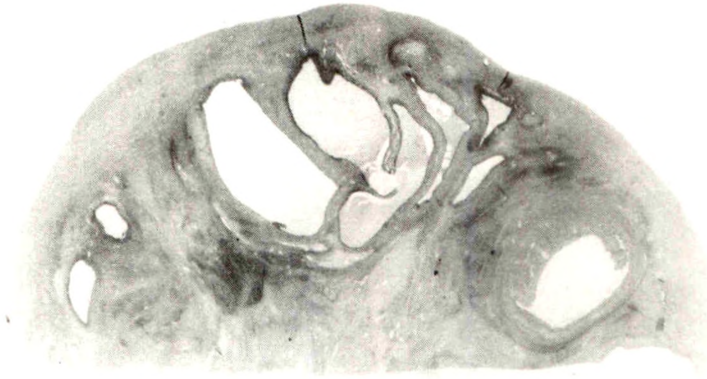

Fig. 1. Patient 1. Right ovary, showing thickened cortex with multiple cystic follicles. Haematoxylin and eosin × 3·4.

These endocrine results suggested the diagnosis of the polycystic ovary syndrome.

She was then anxious to conceive and was treated with clomiphene. She had a withdrawal bleed following medroxyprogesterone acetate, but increasing doses of clomiphene, up to 150 mg/day, failed to induce ovulation and she remained amenorrhoeic.

In March 1983 she was admitted for a laparoscopy. Tubal patency was confirmed. The left ovary was seen to be enlarged to four times the normal size with a thickened glistening capsule; a typical polycystic ovary. In contrast the right ovary appeared normal. Pelvic ultrasound confirmed that the enlarged left ovary had the characteristic appearance of a polycystic ovary containing multiple small (2–4 mm) cysts scattered throughout abundant ovarian stroma (Fig. 3a). The right ovary was of normal size and had normal follicular distribution (Fig. 3b).

Neither the normal nor the polycystic ovary had responded to conventional anti-oestrogen therapy and induction of ovulation remained a problem. In February 1984 we started treatment with 'pure' FSH administered in a pulsatile manner via an automatic infusion pump (Franks *et al.* 1985*a*). In the first cycle a cyst developed on the left ovary, human chorionic gonadotrophin

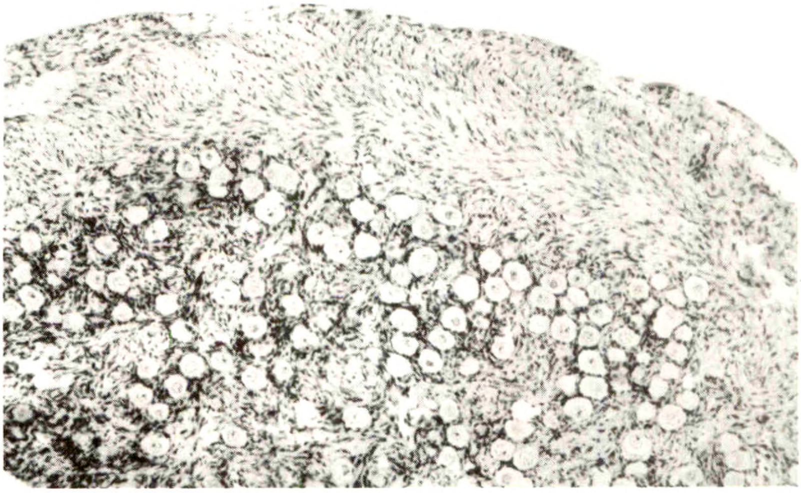

Fig. 2. Patient 1. Left ovary. The cortex is of normal thickness and there are numerous primordial follicles. Haematoxylin and eosin × 94·5

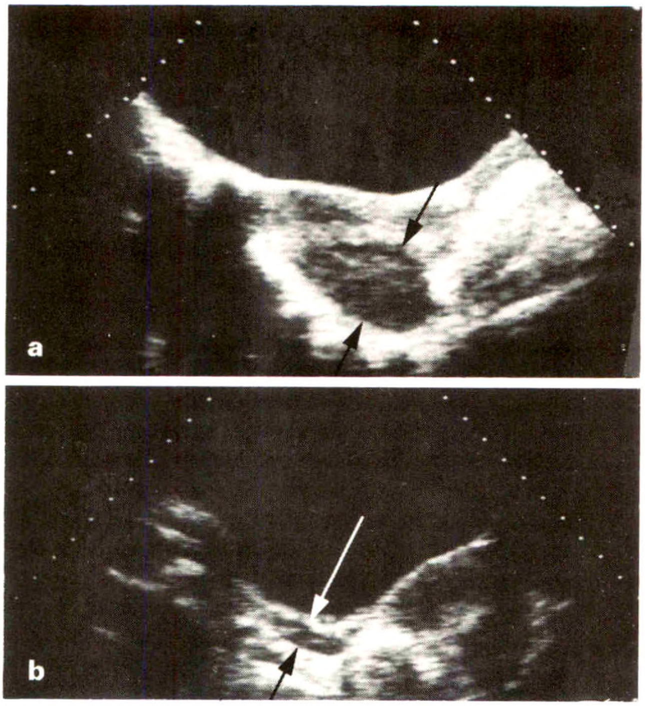

Fig. 3. Patient 2. Transverse sector scans showing (a) enlarged polycystic left ovary and (b) normal right ovary. Centimetre marks shown on diagonal cursor.

(hCG) was administered but there was a short 'luteal phase' and no evidence of ovulation. The second cycle produced multiple follicular development in the normal right ovary. hCG was withheld, the pump discontinued and a period followed 20 days later. She then had two 18-day cycles and then in her fifth cycle a single follicle grew in her right ovary associated with evidence of normal oestradiol secretion. hCG was administered and ovulation confirmed. This resulted in a singleton intrauterine pregnancy which progressed uneventfully to term.

Discussion

The eponym Stein–Leventhal syndrome described a group of women with symptoms of obesity, hirsutism and oligomenorrhoea in whom there was bilateral ovarian enlargement with characteristic ovarian histology (Stein & Leventhal 1935). It soon became evident that these appearances were seen in a heterogeneous group with a spectrum of clinical disorders (Goldzieher & Green 1962). Radioimmunoassay provided some characteristic endocrine indices of the syndrome, but no reliable diagnostic criteria were established. Recent work with high resolution ultrasound has allowed non-invasive identification of ovarian morphology and the recognition of polycystic ovaries (Franks *et al.* 1985*b*).

Bilaterally enlarged ovaries are characteristic of the syndrome, and in our series of over 100 women with polycystic ovaries these are the only two cases in whom only a single ovary was involved.

Unilateral polycystic ovaries have been recognized (Dignam *et al.* 1964; Vejlsted & Albrechtsen 1976; Remouchamps & Ghijsbrecht 1953), but in only two cases has the diagnosis been confirmed by histology (Vejlsted & Albrechtsen 1976; Remouchamps & Ghijsbrecht 1953). In one case a 32-year-old woman with regular ovulatory cycles and proven fertility complained of hirsutism (Vejlsted & Albrechtsen 1976). A bilateral wedge resection was performed and histology of one ovary was normal, whereas the other showed the features of a polycystic ovary. Her hirsutism did not improve. The other case involved a 26-year-old woman who presented with increasing virilization (Remouchamps & Ghijsbrecht 1953).

Laparoscopy revealed a single enlarged ovary which was subsequently removed and found to have a polycystic appearance with a thickened capsule and theca cell hyperplasia. A biopsy was not taken from the opposite ovary but this appeared normal macroscopically and her symptoms resolved following surgery.

Our two patients clearly differ, although in both the initial presentation was lower abdominal pain. In the first patient, this appears to have been due to the enlarged ovary; she had no clinical stigmata of the polycystic ovary syndrome. In contrast the second patient had secondary amenorrhoea and the characteristic endocrinological indices of the syndrome. The presence of unilateral ovarian enlargement was noted at laparoscopy in both patients and the diagnosis confirmed by histology and ultrasound respectively. In the first patient, histology showed no theca cell hyperplasia and this may explain the normal ovarian androgen secretion and absence of signs or symptoms of polycystic ovary syndrome.

An interesting feature in our second patient was the failure of either ovary to respond to anti-oestrogen therapy. If pulsatile FSH treatment had also failed, removing the enlarged ovary was the proposed alternative. It should be noted that ovulation was induced from the normal ovary, rather than the polycystic ovary. This resistance to therapy contrasts dramatically with the picture in our first patient who had regular menses even before oophorectomy and easily conceived subsequently.

There is clearly a diversity of presentation of polycystic ovary syndrome (Goldzieher & Green 1962; Franks *et al.* 1985*b*), whether one or both ovaries are involved. A polycystic ovary should therefore be considered whenever unilateral ovarian enlargement is observed. Pelvic ultrasound can confirm the diagnosis and should be performed routinely, as surgery may be avoided. The aetiology of the syndrome remains unknown (Yen 1980), but the finding of a unilateral polycystic ovary suggests primary intra-ovarian pathology is the cause, at least in these two cases. A disorder caused by an abnormality of hypothalamo-pituitary or adrenal function would be expected to affect both ovaries.

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Characterization of gonadotrophin receptors in a testosterone-producing ovarian androblastoma. Case report

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Case report

A 22-year-old woman of normal habitus (weight 63 kg, height 163 cm) and female karotype was examined because of primary infertility. Menarche had occurred at the age of 14, and since then the menstrual period had varied from 14 to 90 days. The right ovary was slightly enlarged on pelvic examination and ultrasonography revealed an enlarged (35 × 31 × 38 mm) right and normal left ovary. No adrenal tumour was found by computerized tomography. At laparotomy an intracapsular yellowish solid tumour (3 × 3 cm) was excised from the right ovary. The left ovary, uterus and fallopian tubes were normal.

Laboratory investigation

Serum testosterone, sex hormone binding globulin (SHBG), free testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEA-S), oestradiol (E_2), progesterone, 17-OH-progesterone and gonadotrophin concentrations were measured by radioimmunoassays as described by Sieberg *et al.* (1984).

Tumour luteinizing hormone (LH) receptors were assayed as described (Huhtaniemi & Catt 1984), briefly as follows: the tissue was homogenized in Dulbecco's phosphate-buffered saline (pH 7·4) containing 0·1% bovine serum albumin (PBS-BSA). After centrifugation for 10 min at 600 *g* the supernatant was sedimented for 30 min at 20 000 *g*. The membrane pellet was resuspended in PBS-BSA and used for receptor binding studies. Increasing concentrations of ^{125}[I] iodo-hCG (specific activity 70 000 cpm/ng) was added to the membrane suspension, equivalent to 30 mg of tissue, and incubated at room temperature overnight. The reaction was stopped by adding 4 ml of ice-cold PBS-BSA, the membrane fraction was separated by centrifugation, and the bound radioactivity measured. Non-specific binding was measured in the presence of an excess (50 i.u. tube) of unlabelled hCG. Specific gonadotrophin binding under steady state conditions was analysed by the method of Scatchard (1949). After linear regression analysis, the binding capacity and apparent association constant were determined.

For histological studies tumour tissue was fixed for 24 h in phosphate-buffered (pH 7·1) 3·7% formaldehyde. The tissue was then embedded in paraffin, sectioned at 4 μm and stained with haematoxylin and eosin and by the van Gieson method.

Serum homone concentrations before operation are listed in Table 1. Total and free testosterone concentrations were elevated about 1·5- to 3-fold, while serum SHBG was within the normal range. The androstenedione level was normal, but DHEA-S concentration was slightly elevated in three out of eight samples. Serum progesterone and 17-OH-progesterone levels were also high, but E_2 level was within the range of early follicular phase. Also, serum gonadotrophin levels were similar to follicular phase (data not shown).

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Table 1. Serum hormone and sex hormone binding globulin (SHBG) levels in a patient with ovarian androblastoma compared with the normal range observed in fertile women

Hormone	Range (no. of samples)	Normal range
Testosterone (nmol/l)	4·9 – 8·6 (10)	0·7 – 2·8
SHBG (nmol/l)	23 – 48 (8)	17 –91
Free testosterone (pmol/l)	120 –219 (8)	21 –79
Androstenedione (nmol/l)	3·1 – 7·7 (8)	4·9 – 9·0
DHEA-S (μmol/l)	6·2 – 12·4 (8)	2·1 – 9·0
Progesterone (nmol/l)	6·8 – 20 (7)	0·3 – 1·5*
17-OH-progesterone (nmol/l)	3·0 – 19 (6)	0·6 – 3·8*
Oestradiol (nmol/l)	0·17– 0·49 (5)	0·11– 0·44†

DHEA-S, Dehydroepiandrosterone sulphate.
*Follicular phase; † early follicular phase.

Removal of the tumour was followed by an immediate decrease both in right ovarian and peripheral venous testosterone, progesterone and 17-OH-progesterone concentrations (Table 2). The menstrual cycle became normal within 2 weeks of the operation.

The tumour consisted of well-differentiated columnar epithelioid cells growing as hollow and solid tubules (Fig. 1). These cells had oval dark nuclei and a moderate amount of eosinophilic cytoplasm and were reminiscent of Sertoli cells. In the interstitial stromal tissue there were lipid laden macrophages and a few well-developed Leydig cells.

A 20 000 **g** membrane fraction of the tumour bound hCG specifically. Scatchard analysis indicated an equilibrium association constant (K_a) of $2{\cdot}5\times10^{10}\,\mathrm{M}^{-1}$ and a binding capacity of 142 fmol/g of original tissue (Fig. 2).

Discussion

Gonadotrophins are bound to specific high affinity ovarian receptors. This is followed by the activation of adenylate cyclase and an increase in cAMP production which activates target cell responses. Some ovarian tumours may serve as target tissues for gonadotrophins, because the incidence of ovarian neoplasms is increased around the menopause in the presence of high circulating gonadotrophins (Longo & Young 1981) and prolonged treatment with gonadotrophins (Biskind *et al.* 1953) and constantly elevated levels of gonadotrophins in rodents can induce ovarian tumours (Kammerman *et al.* 1977). Furthermore, gonadotrophins are bound to human ovarian neoplasms (Warlaw *et al.* 1975; Davy *et al.* 1977; Kammerman *et al.* 1981; Rajaniemi *et al.* 1981*a*). One of the most detailed investigations indicates absence of gonadotrophin receptors in epithelial tumours, but presence of FSH receptor in a neoplasm from the hormone producing ovarian compartments (Stouffer *et al.* 1984).

Androblastoma accounts for less than 0·5% of all ovarian neoplasms. It is seen most often in

Table 2. The levels of testosterone (T), progesterone (P), and 17-OH-progesterone (17-OH-P) in peripheral and ovarian venous serum before and after the removal of the right ovarian androblastoma

		Postoperative							
Hormone	Pre-operative	30 min	3 hours	1 day	2 days	3 days	4 days	5 days	7 days
Peripheral serum									
T (nmol/l)	4·9	3·0	1·8	0·6	0·5	0·5	0·4	0·7	1·0
P (nmol/l)	20	12	10	1·7	0·7	0·5	0·5	0·7	0·6
17-OH-P (nmol/l)	19	14	14	3·6	2·8	3·3	1·9	5·4	5·5
Ovarian vein									
T (nmol/l)	8·5	3·3							
P (nmol/l)	53	16							
17-OH-P (nmol/l)	28	19							

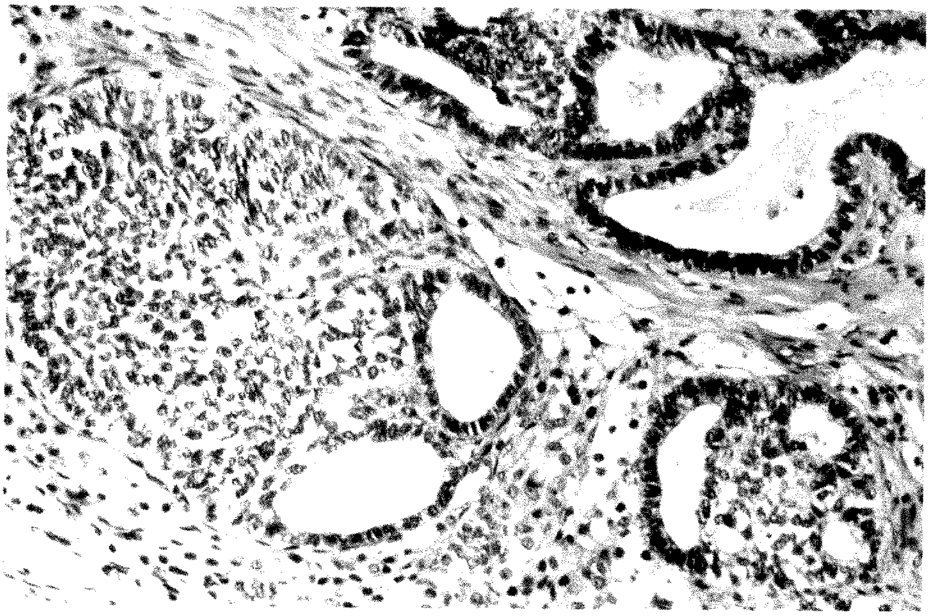

Fig. 1. Histology of ovarian tubular androblastoma. The characteristic Sertoli cell-like columnar epithelioid cells form solid and hollow tubules, and in the stroma there are lipid containing macrophages and a few Leydig cells. Haematoxylin and eosin staining ×250.

young women, who usually become virilized and develop oligomenorrhoea and/or amenorrhoea.

Our patient had irregular menstruation and constantly elevated serum testosterone, progesterone and 17-OH-progesterone levels and normal serum androstenedione and DHEA-S concentrations but no clinical signs of hyperandrogenism. Removal of androblastoma caused an immediate decrease both in peripheral and ovarian venous testosterone, progesterone and 17-OH-progesterone concentrations and normalization of the menstrual cycle. This suggests that the tumour was responsible for the production of these steroids.

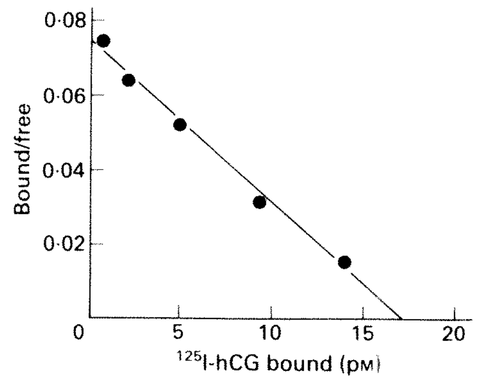

Fig. 2. The Scatchard-plot analysis of gonadotrophin receptors in the membrane fraction of a tubular androblastoma. Each point is the mean of triplicate measurements.

The most interesting finding in our patient was the presence of a tumour receptor able to bind hCG with high affinity and low capacity. The characteristics of these binding sites were very similar to those in the ovaries of healthy women during follicular and luteal phase (Halme *et al.* 1977; Rajaniemi *et al.* 1981*b*). Thus we can add androblastoma to the ovarian tumours that may have gonadotrophin receptors. Their presence suggests that the growth and/or hormonal activity of androblastoma may be affected by LH.

Acknowledgments

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Conservative treatment of epithelial ovarian cancer in a 19-year-old girl. Case report

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Case report

A 19-year-old nulliparous unmarried Asian girl presented to the general surgical unit on 28.5.81 with a 2-month history of generalized abdominal distension and constant pain which had localized to the right lower quadrant and become severe in the last 2 weeks before admission. She had no gynaecological symptoms, her periods were regular and she had never had intercourse. The abdomen was grossly distended, tense and dull to percussion centrally with no clinical evidence of ascites. There were no other abnormal signs. The provisional diagnosis was of a large benign ovarian cyst.

A laparotomy was performed by a general surgeon on 1.6.81 through a Pfannenstiel incision. A huge smooth-capsuled non-adherent left ovarian cyst completely filled the entire abdominal cavity. There was no free fluid. The cyst was aspirated through a purse-string suture and 10 litres of mucoid fluid were drained. There was some peritoneal spill. A left oophorectomy was performed. The right ovary was conserved but contained a small cyst. The abdominal cavity was otherwise normal. The aspirated ovary measured 20 × 16 × 8 cm and weighed 740 g. Histologically the tumour was a well-differentiated papillary mucinous cystadenocarcinoma with no capsular invasion but with some small foci of poorly differentiated adenocarcinoma. The clinical staging was FIGO stage I(a)i.

Postoperatively one of us (M.K.D.) was consulted regarding her further management. The patient was determined to maintain her fertility despite the risks which were explained.

Because the right ovary had been cystic a staging laparotomy was performed on 25.6.81. There was no ascites and the peritoneal surfaces including the subdiaphragm were normal as were the omentum and the para-aortic nodes. Washings were taken and a large wedge biopsy of the right ovary showed no evidence of malignancy on frozen section (confirmed later histologically). The peritoneal washings contained no malignant cells. Postoperatively a baseline lymphangiogram and carcinoembryonic antigen (CEA) level were normal. It was decided to follow her with 6-monthly laparoscopies initially and the first, on 10.3.82, was normal.

Before the next laparoscopy could be organized she became pregnant. The pregnancy was uncomplicated and ended in the spontaneous vaginal delivery at term of a 3080 g female infant. CEA levels and ovarian ultrasound scans were normal throughout. She became pregnant again before the next laparoscopy was arranged. This time she had an assisted breech delivery at term of a 3270 g female infant. Ovarian scans and CEA levels remained normal. On 8.8.84 she was admitted for a follow-up laparoscopy which showed no obvious recurrence and there were no abnormal cells in peritoneal washings. Aware of the risks, the patient stated that she wanted one more pregnancy if possible, as she wanted a son. Consequently the 6-monthly laparoscopies were continued and total abdominal hysterectomy, salpingo-oophorectomy and omentectomy were planned to follow her next confinement.

A further spontaneous vaginal delivery occurred in June 1985. A live male infant was born weighing 3700 g. In October 1985 she had a total abdominal hysterectomy, bilateral salpingectomy, right oophorectomy and omentectomy. There was no evidence of recurrent tumours. Peritoneal washings were taken. Her recovery was uneventful.

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There was no histological evidence of malignancy in the operative specimens. There were follicular cysts in the ovary and a uterine polyp consisting of old hyaline decidual tissue. The peritoneal washings were normal when examined cytologically.

Discussion

Epithelial ovarian malignancies are rare during childhood and adolescence. Norris & Jensen (1972) found only three true epithelial cancers in their review of 353 cases of ovarian malignancy in females under the age of 20. Morrow (1981) points out that most of the 1·1% of ovarian malignancies occurring before the age of 20 are germ cell tumours and a diagnosis of epithelial cancer 'must be viewed with great circumspection'.

The treatment for FIGO stage I(a) ovarian cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy with greater omentectomy (Parker *et al.* 1970). Unilateral oophorectomy is seldom performed intentionally as definitive surgery for frank ovarian carcinoma. As in this case it is usually the pathologist who presents the surgeon with the dilemma. In a young nulliparous woman in whom the histological diagnosis is in doubt at operation conservative surgery is the procedure of choice. The risk of a second operation is justified to exclude further evidence of malignancy (Munnell 1969). Fertility and endocrine function must be balanced against survival. Although several authors have suggested a better prognosis in younger women, the overall survival rate in stage I(a) ovarian cancer is still only 67·8% (Morrow 1981). Simple oophorectomy has been recommended in young women who are interested in pregnancy and accept the risks as in this case (Wiltshaw 1981). But what are the risks?

Munnell (1969), reviewing the literature and his own series, found no statistically significant difference in survival rates when comparing conservative with traditional radical surgery. However, as survival rates were slightly higher in the radically treated groups he favoured radical surgery in all but the well differentiated mucinous carcinomas. He joined with Kottmeier (1968) in urging caution with serous cancers. Mucinous carcinomas have a more favourable prognosis generally as at least half the carcinomas are confined to the ovary, less than 10% are bilateral and surface involvement is uncommon (Hart 1981). Other authors (Decker *et al.* 1973; Williams & Dockerty 1976) have shown that the histological type is not important compared with the stage and grade of the ovarian cancer. Webb *et al.* (1973) found that the 5-year survival rate dropped from 89% with complete surgery to 67% for conservative surgery, but noted that the 13 patients in his study who were treated with unilateral oophorectomy were not a homogenous group. He identified some poor prognostic features that lowered the survival rate to 68% with surface excrescences, 56% with rupture of the cyst and 51% with adherence of the cyst. Williams *et al.* (1973) observed a 74% survival rate with conservative treatment in low grade intracystic non-ruptured non-adherent tumours but re-emphasized the poor prognosis with rupture of the cyst and extracystic disease. Despite the fact that aspiration here was carried out under controlled conditions, a certain amount of peritoneal spill was unavoidable. It has been well demonstrated that survival rates may be decreased by 50% when peritoneal spill occurs (Williams *et al.* 1973; Purola & Nieminen 1968; Webb *et al.* 1973). Controlled tapping was performed in this case to limit the size of the incision, to provide better exposure and to avoid uncontrolled rupture in what was thought to be a benign cyst.

Even though the maintenance of fertility should be the only real justification for conservative therapy, there is little data on subsequent pregnancies in these patients. Williams *et al.* (1973) reported 12 pregnancies in seven patients and Munnell (1969) 10 pregnancies in six patients. This probably reflects the age distribution of the patients in these reviews, as very few are under the age of 30, and it has been reported that wedge biopsy can cause mechanical infertility (Weinstein & Polishuk 1975) and ovarian failure (Oelsner *et al.* 1975).

Morrow (1981) states that the minimum requirement for conservative surgery in ovarian cancer is a stage I(a)i tumour (i.e. a unilateral unruptured tumour with no adherence, no surface excrescences and no ascites), with adequate surgical-pathological investigation (i.e. well-differentiated, with negative peritoneal washings and biopsies, negative omentum and negative wedge biopsy of the residual ovary). Williams & Dockerty (1976) stressed the importance of biopsy of the contralateral ovary as they noted that the occurrence of bilateral involvement was high in their series despite the macroscopic appearance or histological type. The patient must have full knowledge of the risks involved which must be very small using the above protocol, but there is no real prospective data to hand. Because of the long-term risk of recurrence shown by Williams *et al.* (1973) it was recommended that definitive surgery was carried out when childbearing was completed.

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CORRESPONDENCE

Womens' views on keeping fetal movement charts

Dear Sir,

Since the recognition of the fact that reduction or cessation in maternally perceived fetal movements may precede intrauterine death by a day or longer (Sadovsky & Jaffe 1973) and development of the Cardiff 'count to ten' chart (Pearson & Weaver 1976) there has been a great deal of work on validity, correlation with other means of fetal monitoring, ease of administration and cost effectiveness of daily fetal movement count (DFMC) but little on women's reaction or indeed on how best to utilize DFMC. I therefore welcome the study by Draper *et al.* [*Br J Obstet Gynaecol* (1986) **93,** 334–338] and their recommendation that practitioners must explain to the women the importance of noting abnormal fetal movement patterns and that they must report these abnormal patterns at once.

I describe below a single case where such an explanation may have prevented a stillbirth and offer further suggestions on possible measures to improve the usefulness of DFMC.

A 30-year-old primigravida, a research scientist, was admitted to a London teaching hospital at 38 weeks gestation with total absence of fetal movement of 18 h duration. The patient, a potential diabetic, had had a threatened abortion at 8 weeks and scans at 8 and 17 weeks had shown a marginally small-for-dates baby. Clinically the baby was of 'good size', the fetal head was not engaged; and cardiotocograms showed a reactive fetal heart rate pattern. The patients recorded 10 kicks in 7 h and in 1 h respectively over the next 2 days, starting at 09.00 hours. She described the character of fetal movements as 'writhing'.

The patient was discharged with instructions to maintain a kick chart and return for another cardiotocogram 5 days later. She was reassured that it was common for fetal movements to decrease over the last weeks of pregnancy, that it was not known what had caused the baby to be sleepy but there was nothing to worry about.

The patient returned 40 h later and reported gradual stoppage of 'writhing movements' 8 h earlier. Intrauterine death was confirmed with a post mortem diagnosis of intrauterine growth retardation with placental insufficiency. When asked why she did not report earlier, she described being immensely reassured by explanations given to her and that she did not wish to be neurotic about what had appeared to be a false alarm during the previous admission.

While criticism of some aspects of the management of this pregnancy is readily accepted, I feel that several important issues emerge from it. (i) I endorse the recommendation of Draper *et al.* (1986) that clear explanation about the possible causes of diminution of fetal movements and instruction to report any abnormality immediately must be given to the patient. A leaflet discussing why and how a DFMC may be useful could accompany a Cardiff kick chart. (ii) The value of the instruction on the Cardiff kick chart for patients to report if fewer than 10 movements are felt between 09.00 and 21.00 hours is clearly debatable. (iii) It is recognized that the movements of a growth-retarded fetus (at risk) are less in number and duration leading to slow and monotonous movement patterns (Bekedam *et al.* 1985). The significance of a change in the character of fetal movements must be discussed with the women. (iv) While accepting the importance of reassurance to a worried patient, I feel that euphemisms such as 'sleepy' or 'lazy' baby and 'nothing to worry about' should be used with caution, if at all. (v) I also feel that there may be room for discussion about the association of fetal movement patterns and its well-being at parentcraft lectures, which are in wide use in most obstetric units in this country.

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Results of donor insemination related to specific male infertility and unsuspected female infertility

Dear Sir,

When women present for artificial insemination (AI), if they fail to conceive at the first cycle, they are usually re-inseminated at their next cycle, and this process is repeated until either conception or drop-out. Foss & Hull [*Br J Obstet Gynecol* (1986) **93**, 275–278] present interesting data on a large number of AI conceptions, relating the probability of success to the order of the insemination (1st, 2nd, 3rd . . .). These probabilties do not decline appreciably over the first six inseminations. As the authors note, this is in marked contrast to natural insemination, in which the monthly conception probabilities fall sharply across the first 6 months. This latter fall, as the authors remark, is due both to heterogeneity of fecundability between women, and to a decline in fecundability within individual women (due, *inter alia*, to declining coital rates).

Now since one may presume that there is heterogeneity of fertility status between women presenting at an AI clinic, one would expect that probabilities of success in successive inseminations would decline (because the most fecund women would eliminate themselves first by getting pregnant).

This being so, one is led to suggest that there must be some sort of countervailing influence acting on individual women slightly to enhance their probability of pregnancy at successive inseminations.

Anxiety has been shown to prevent (Drillien 1946 or delay (Peyser *et al.* 1973) ovulation. I suggest that the anxiety felt by (some) women undergoing AI diminishes at each repetition, thus slightly increasing the probability of conception. There are frequent references in the literature to clinical impressions of psychological influence on the hypothalamic-pituitary-ovarian axis. The data of Foss & Hull (1986) seem to lend statistical support to these impressions.

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The pill does not cause 'thrush'

Dear Sir,

We were interested to read the report of the study by Davidson & Oates [*Br J Obstet Gynaecol* (1985) **92**, 1265–1266] which confirmed the findings of our own study carried out in 1500 women attending the Family Planning Centre, Edinburgh (Goldacre *et al.* 1979). In that study, although fungi were isolated in 21% of women, we found no association between the use of the pill and the isolation of either *Candida albicans* or other fungi.

We recognize the limitations of our study and that of Davidson & Oates (1985) in that both deal with cross-sectional data so that some of the women in each study may have stopped taking the pill because of trouble with *Candida* infection in the past. However, in our study a history was taken of each woman's past symptoms and their treatment and there was no obvious evidence to support this.

We found that users of barrier methods had just as high a prevalence of *Candida albicans* as pill users and a higher prevalence of other fungi than in women on the pill. These data correlate with the findings of Davidson & Oates (1985) in relation to users of 'other methods'. We believe that this is because women re-infect themselves when they start using the diaphragm again after treatment for fungal infections. It is now our practice to advise women using occlusive pessaries who develop fungal infection, to wash the cap in hypochlorite solution and rinse it thoroughly before starting to use it again after completing a course of therapy.

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Authors' reply

Dear Sir,

We apologize for not referring to the work of Goldacre *et al.* (1979) which somehow escaped searches, although we are glad to see that in general terms it confirms our work.

There was no evidence in our study that a significant number of women had changed their contraception due to candidosis. Most patients attending had come for other reasons and a large percentage of our patients took the oral contraceptive pill.

Our most interesting finding was that the signs and symptoms of candidosis were unexpectedly disassociated. Symptoms were not necessarily associated with the presence of the fungi. (Davidson & Mould 1978) leading us to the conclusion that *Candida* was always a secondary organism. In our clinic it was significantly associated with other infections such as *Chlamydia trachomatis,* genital herpes and especially wart virus infection.

Candida was also associated with chemical damage of vagina and vulval epithelium and we feel that it is possible that recurrences in diaphragm-users are as likely to be associated with the spermicide or other infections in this highly sexually active group rather than re-infection from the diaphragm. The seed must, of course, be present but the soil is all important in clinical candidal infection.

It would be interesting to note if disinfection of the diaphragm leads to improvement in the relapse rate of patients.

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A syndrome ot liver damage and intravascular coagulation in the last trimester of normotensive pregnancy. A clinical and histopathological study

Dear Sir,

It is quite astonishing that a paper [*Br J Obstet Gynaecol* (1986) **93,** 145-155] dealing with disturbed hepatic function in the third trimester makes no mention of acute fatty liver of pregnancy (AFLP) in the differential diagnosis. The more so, as AFLP includes among its presenting features epigastric pain, derangement of liver enzymes, thrombocytopenia, coagulation disturbances (including DIC), as well as blood pressure measurements that are often normal or only slightly elevated and proteinuria that may be minimal or absent (Hague *et al.* 1983). Antithrombin III levels have also been found to be low (Laursen *et al.* 1983). In this paper by Aarnoudse *et al.* 1986), uric acid levels are neither recorded nor discussed, although they are a well-established diagnostic indicator in both pre-eclampsia and AFLP (de Swiet 1985). The characteristic histological feature in AFLP of hepatic microsteatosis in a periportal distribution may be missed unless specific staining for fat is carried out (Kaplan 1985); focal necrosis is also seen in some cases (Burroughs *et al.* 1982). One of the reference group of mothers had a twin pregnancy—AFLP has a higher incidence in multiple gestation (Hague *et al.* 1983), while it would have been of interest to know the sex of the infants (Hague 1982). To be fair to the authors, Weinstein (1982, 1985) did not discuss AFLP in either of his two papers on the so-called HELLP syndrome.

We believe that AFLP and pre-eclampsia form part of a spectrum of pregnancy related disorders which may be mild or catastrophic (de Swiet 1985). We urgently need more information about the milder presentation of AFLP, in particular relating hepatic histology to modern techniques of hepatic imaging such as ultrasound, computerized tomography and nuclear magnetic resonance. While there are many useful data in this paper, there is much more that could have been said or done.

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Aarnoudse, J. G., Houthoff, H. J., Weits, J., Vellenga, E. & Huisjec, H. J (1986) A syndrome of liver damage and intravascular coagulation in the last trimester of normotensive pregnancy. A clinical and histopathological study. *Br J Obstet Gynecol* **93,** 145-155.

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Authors' reply

Dear Sir,

Although it was not the aim of our paper to present a thorough report on the differential diagnosis of disturbed hepatic function in the third trimester of pregnancy, acute fatty liver of pregnancy (AFLP) as a differential diagnostic possibility might have been taken into consideration in the discussion of our paper. If this had been the case, it only would have been to reject the diagnosis AFLP for all cases included in this study, because the laboratory and histopathological findings made the diagnosis of AFLP seem very unlikely. The characteristic elevation of white blood cell counts above 15 000 in AFLP (Kaplan 1985) was not observed in our patients. Despite a considerable increase in liver enzymes, the bilirubin levels were normal in all except two who showed only a mild elevation. Microscopically, the specific lesions of AFLP include a swollen or foamy appearance of the hepatocytes in the third acinar zone around the terminal hepatic venules, together with a variable amount of acinar inflammation and patchy liver cell necrosis. A fat stain on cryostat sections may further reveal the fatty infiltration of the cells. In contrast, in the biopsies of the patients in our study the pathological alterations were predominantly periportal and directly related to sinusoidal coagulation. In the cases with mild pathological changes in the periportal areas, a fat stain has been performed on cryostat sections in conjunction with the fluorescence microscopy to differentiate between intravascular coagulation on the one hand and fatty infiltration of

AFLP on the other, where the latter always proved to be essentially negative.

Regarding the question about the uric acid levels in our patients, we found elevated serum uric acid levels in all 13 patients (range of peak values 0·43–0·71 mmol/l).

In conclusion, so far our findings do not contain any substantial evidence for AFLP, as suggested by Hague and de Swiet. We agree, however, that more information about the milder presentation of AFLP is urgently needed.

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Effect of epidural analgesia on maximum and minimum blood pressures during the first stage of labour in primigravidae with mild/moderate gestational hypertension

Dear Sir,

The paper by Greenwood & Lilford [*Br J Obstet Gynaecol* (1986) **93**, 260–263] cannot be allowed to pass without comment.

We would disagree initially with their title describing gestational hypertension, while later on they state that 'the presence of .... proteinuria .... did not form part of the selection criteria'. Gestational hypertension is characterized by the development of hypertension (but not proteinuria) in women who are apparently normotensive at the beginning of pregnancy but have a strong family history of hypertension (Chesley 1980; Davey 1985). Hence, it is obvious that they are comparing one mode of treatment in two different conditions without specifying the results for each group, a manoeuvre that seriously undermines the validity of their paper.

As a retrospective study there is no standardization of blood pressure measure and no allowance for the effects of caval or aortic compression (Crawford 1979) nor is the effect of importance of arm position taken into account (Webster *et al.* 1984). Failure to standardize the technique to allow for these factors must magnify the already large observer variation present in any trial involving blood pressure measurements.

The efficacy of the epidural anaesthetic was not discussed, apart from the blithe assumption that waiting 30 min after its stated time of administration guaranteed it would have taken effect. The hypotensive effect of an epidural is probably related to its vasodilatory effect, the degree of which varies with the intensity and number of segments blockaded—another point ignored in their paper. It is interesting that the patients underwent fluid preloading before epidural analgesia, presumably to prevent maternal hypotension leading to abnormal fetal heart rates (Collins *et al.* 1978). Might this not have contributed to the failure to reduce maximum blood pressure?

In their discussion regarding the effect of epidural analgesia on uteroplacental blood flow they state that 'any benefit may be offset by the deleterious effects of intermittent vasoconstriction'. This surely is standing the argument on its head, as the uteroplacental blood flow is increased by epidural analgesia above the background level. This must be better, if only intermittently, than no increased flow at all.

In conclusion we would continue to advocate the use of epidural analgesia for patients with hypertension, if only for the proven improvement (Jouppila *et al.* 1982) in uteroplacental blood flow. Further, better studies are required to assess the value of epidural analgesia in controlling maximum blood pressure.

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Jouppila, P., Juoppila, R., Hollmén, A. & Koivula, A. (1982) Lumbar epidural analgesia to improve intervillous blood flow during labour in severe pre-eclampsia. *Obstet Gynecol* **59**, 158-161.

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Authors' reply

Dear Sir,

While appreciating their interest, few of the comments by Page and Johnston detract from the validity of our paper. If is a pity to become bogged down in the definitions of hypertension in pregnancy as there are almost as many of these as there are workers in the field. From their experience of working in this country, it must surely have been quite clear to the writers that the reason for lumping proteinuric and non-proteinuric late pregnancy hypertension together, in keeping with other authors (James & Davies 1976), was that our survey included very few of the former. It is, of course, possible that patients with severe, proteinuric, pre-eclampsia would have a different response but inability to establish this point does not invalidate our paper any more than the discovery of aplastic crisis invalidated the original observation that the reticulocyte count rises in haemolytic anaemia. It is possible, though not likely, that subsequent observations will show that maximum blood pressure can be reduced by intermittent lumbar epidural in patients with severe proteinuric hypertension. In the meantime our point that it is quite illogical to use this form of analgesia as a hypotensive agent is surely well supported.

The writers of the letter seem greatly concerned about the standardization of the blood pressure measurement. While we fully concede that the precision of our measurements could be enhanced in a prospective study, this does not affect the overall accuracy of our conclusions. Thus the same lack of standardization applied to both the control and the study groups and to patients before and after epidural analgesia. Like all other authors we showed a drop in mean and minimum blood pressures. In addition, however, we showed that there is no drop in maximum blood pressure. This is not a result of poor standardization but because we were the first group to examine this variable.

The writers were also exercised because we did not state the efficiency of the epidural analgesia. First we were looking at its effect under operational circumstances and not some artificial, contrived situation. Our conclusions are valid for standard medical practice. Page and Johnston go on to worry about the number of segments blocked and the duration of analgesia before blood pressure measurement. As we were writing a journal article not a text book and as knowledge of these factors would not alter the validity of our conclusions they were justifiably omitted. The technique at Queen Charlotte's Hospital is fairly standard and brought about the well-known drop in blood pressure after epidural block. If we had made the unusual claim that there was no drop in blood pressure, then the writers' concerns would be justified. As if all is not enough, the writers then waste further energy wondering whether the unaltered maximum blood pressure was due to preloading. Of course, this is quite possible and it was for this reason that we mentioned this aspect of practice in the method selection. However, since preloading is carried out by most authorities including Jouppila (Jouppila *et al.* 1982), subsequently quoted by the writers, and since this method reduces the incidence of hypotension, especially in pre-eclamptic patients, we feel that the practical importance of our observation holds good.

In rejecting the bulk of their letter, replete as it is with epidemiological confusion, we should be careful not to throw the baby out with the bathwater, for at the end of their letter the authors make an interesting point. Relying heavily on the data of Jouppila *et al.* (1982) they advocate epidural analgesia, not because of its hypotensive effect, but for its effect on placental blood flow. This, in itself, is a conceptual advance but the writers worry us greatly by recommending this for all patients with hypertension. Thus more careful reading of Jouppila *et al.* (1982) would have shown that these beneficial effects, demonstrated by radioisotope clearance, pertain to patients with severe proteinuric hypertension. It is only these patients who retain muscular and reactive spiral arteries (de Wolf *et al.* 1980). In other patients epidural analgesia lowers fetal oxygen tension (Rooth, personal communication), possibly because of shunting of blood towards the myometrium. Thus any argument that epidural analgesia should be used for its effect on intervillus blood flow, must be confined to a small group with proteinuric hypertension. Even in these patients the arguments for this method are not as clear-cut as the writers indicate. Again careful reading of Jouppila *et al.* (1982) would have shown that the findings apply to a period 10 or 20 min after the onset of analgesia when vasodilatation is maximal. The beneficial effects are therefore intermittent. In addition, this must be weighed against the damaging effect of postural hypotension which is encountered more frequently in pre-eclamptic patients. Our article shows quite clearly that we were well aware of the possible short-term beneficial effect of epidural analgesia in severe pre-eclampsia and we quoted Jouppila's work ourselves. We, however, made the more logical suggestion that continuous epidural analgesia and other vasodilatory agents should be investigated for this purpose. A more recent report by Jouppila *et al.* (1986), using Doppler ultrasound, showed that labetalol may increase intervillous flow although this did not reach statistical significance, possibly due to the very small sample size. Similarly nifedipine relaxes placental arterioles (Maigaard *et al.* 1984) and although the tocolytic effects of this agent preclude intrapartum use, this research shows the direction that future treatment will take.

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Maigaard, S., Forman, A. & Andersson, K.-E. (1984) Effects of nifedipine on human placental arteries *Gynecol Obstet Invest* **18**, 217-224

British Journal of Obstetrics and Gynaecology
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BOOK REVIEWS

Fundamentals of Obstetrics and Gynaecology, Fourth Edition Vol. 1 Obstetrics, Vol. 2 Gynaecology by Derek Llewellyn-Jones. Faber Paperbacks, London, Boston, 1986, Vol.1 502 pages, £12.50, Vol. 2 315 pages, £9.95

The Fourth Editions of well-known textbooks are not always reviewed by Journals. The First Edition of these books came out in 1969 and in the 16 years since, Llewellyn-Jones has revised them three times. Since it is one of the most popular textbooks for undergraduates, it is perhaps wise to reassess it during its middle-age. Textbooks of obstetrics and gynaecology should live with their authors, starting when the writers are firebrands and becoming established teachers; the books continue into the accepted stage when the author is a known authority, in perhaps fewer subjects, and they should finish when the author closes his clinical career and his teaching is becoming based upon events of the past. There are no signs that Llewellyn-Jones' book is entering its third phase but it is probably in the second phase now with Llewellyn-Jones an established and well-loved teacher of the subject.

Obstetrics started as a first aid subject, rescuing babies from awkward corners; it is now a science in its own right. Llewellyn-Jones grafts this in as he goes, so that the book contains more and more basic science of the subject. This is not put in introductory chapters but is fed in throughout the whole volume, thus giving interest to the student. Perhaps more can be given to the emphasis now of placental bed blood flow as an important mechanism in exchange across the placenta. This is probably a more important cause of intrauterine growth retardation than poor exchange across placental membranes which was last decade's theory. The algorithms are helpful in many cases but one wonders whether culdocentesis is still the major method of diagnosis of ectopic pregnancy. From its position in the algorithm on p. 297, it would seem that Llewellyn-Jones thinks so but in his text obviously he does not emphasize it. The diagrams are a pleasure to see and we are glad that Llewellyn-Jones still has the services of Mrs Audrey Besterman for she has illuminated much of what he has said in the past and the present.

In the volume on gynaecology, we are shown how the subject has moved from being a Germanic, mechanical set of diseases treated by operations into a socio-biological one, in which much more attention is paid to the background environment of the woman and her hormonal *milieu interieur*. Sexual problems, contraception and screening are now major fields in gynaecology and Llewellyn-Jones emphasizes these in his new edition. The problems of fertility are well dealt with and he keeps his books slim by leaving details of surgical treatments to postgraduate volumes.

There is a good bibliography at the end of each chapter, where Llewellyn-Jones gives a series of articles which would be helpful. We have checked many of these and find them mostly up-to-date. There are some rather older articles still quoted which perhaps could be removed and replaced with new ones.

The reviewer is mystified by the use of colour in the printing of this book. It appears on p. 32 and p. 67; the reviewer cannot find it elsewhere. Since histology slides are always seen in colour, perhaps some extension could be made for these to be colour printed without any great increase in costs for what is rightly a popular book.

These are still first-rate volumes and can be recommended to any undergraduate studying the subject for the first time. They are well-written, well-illustrated and the pair of volumes deserves to be widely read.

Geoffrey Chamberlain

Infection in the Female. Second edition by William J. Ledger. Lee & Febiger, Philadelphia, 1986, 293 pages with figures and tables, $42.25

In this book the author attempts to provide a rational approach to the care of the woman with a gynaecological or obstetric infection. He finds that many medical schools have relinquished the teaching of the relation of micro-organisms to disease in favour of cellular biology, resulting in a lowering of the standard of patient care in this field with increasing medical mishaps terminating in suits for malpractice.

The book has a refreshingly different approach, starting with classification of micro-organisms which cause infection, the collection of specimens suitable for examination, anti-microbial drugs, host response to infection, and clinical aspects which are divided into community and hospital acquired infections together with one chapter on maternal infection with adverse fetal and newborn outcomes.

The American origin of the book is reflected in the choice of antimicrobial therapy with clindamycin and an aminoglycoside regarded as the gold standard of therapy of soft tissue pelvic infection and an undue emphasis on the value of cephalosporins. The overall approach is, however, rational without the 'kill all known germs' obsession found in much American writing. As with all transatlantic publications, British readers will find the parochial selection of references a source of irritation.

The description of vaginal infections and vaginosis do not reflect the more recent advances which have taken place in the understanding of these conditions and the sections of tuberculosis and, particularly, actinomycosis are disappointing. *Actinomyces bovis* is not a human pathogen and of the others which are only *A. israelii* is mentioned. *Chlamydia trachomatis* is not given its full name but merely its generic title.

Despite these few quibbles this easy-to-read book provides an excellent review of infection and should be read by all who have the clinical care of patients. Those particularly interested in the subject will benefit from having Bill Ledger's work constantly to hand as a ready source of information.

Stanley Seligman

The Kidney in Pregnancy edited by Vittorio Andreucci. The Martinus Nijhoff Publishers, The Netherlands, 1986, 236 pages with figures and tables, £49.00, Dfl 220.00, $59.95

The question which must be answered for any new book on a well covered subject is—is it needed? I have to say that this book is not needed. Let me try to justify that harsh statement.

Frist, a sizeable component of the book is not about the kidney at all, but about such aspects of the hypertensive complications of pregnancy as pathogenesis, treatment, and associated coagulation disorders. It is true that the renal aspects of pre-eclampsia are also dealt with, but almost half the book is devoted to aspects of hypertensive complications, including pre-eclampsia, which the interested reader will find much more effectively covered by such recent classics as Leon Chesley's 'Hypertensive Disorders of Pregnancy'.

Other renal problems associated with pregnancy, acute renal failure, dialysis and the renal transplant have been covered in greater depth in an excellent issue of Kidney International August 1980, and by a 'Seminar in Nephology' published in 1984.

Although it is clear from the overlap of chapters that contributors had little editorial direction, the book is not basically bad. There are some interesting and excellent essays, on the normal kidney by John Davison, on proteinuria by Priscilla Kincaid-Smith and her colleagues, and on urinary tract infection by Iain McFadyen; we just don't need another expensive book of this kind.

F. E. Hytten

Books received some of which may be reviewed at a later date

Reproductive Failure edited by Alan H. DeCherney. Churchill Livingstone, Edinburgh, 1986, 308 pages with figures and tables, £39.00

Pineal Research Reviews Volume 4, edited by Russel J. Reiter. Alan R. Liss, Inc., New York, 1986, 266 pages with figures and tables, £62.00

Drugs in Pregnancy and Lactation. A Reference Guide to Fetal and Neonatal Risk Second Edition by Gerald G. Briggs, Roger K. Freeman & Sumner J Yaffe. Williams and Wilkins, London, 1986, 537 pages with figures and tables, £43.00

Ultrasound in Perinatology (Clinics in Diagnostic Ultrasound 19) edited by Nabil F. Maklad. Churchill Livingstone, Edinburgh, 1986, 224 pages with figures and tables, £27.50

Standardization and Quantitation of Diagnostic Staining in Cytology edited by Mathilde E. Boon & L. P. Kok. Coulomb Press, Leyden, 1986, 159 pages with figures and tables, Dfl 99.00, US$ 40.00

With Child. Birth Through the Ages by Jenny Carter & Thérèse Duriez. Mainstream Publishing, Edinburgh, 1986, 286 pages illustrated, £12.95

Clinical Obstetrics: A Public Health Perspective edited by Benjamin P. Sachs & David Acker. PSG Publishing Company, Inc., Massachusetts, 1986, 308 pages, £28.00

Breast Disease (Contemporary Issues in Obstetrics and Gynecology Volume 1) edited by Douglas J. Marchant. Churchill Livingstone, Edinburgh, 1986, 169 pages with figures and tables, £32.00

Principles of Medical Therapy in Pregnancy edited by Norbert Gleicher. Plenum Medical Book Company, New York, London, 1986, 1290 pages with figures and tables, $125

Colposcopy: A Scientific and Practical Approach to the Cervix, Vagina and Vulva in Health and Disease Third Edition by Malcolm Coppleson, Ellis Pixley & Bevan Reid. Charles C. Thomas, Publisher, Springfield, Illinois, 1986, 581 pages with figures and tables, $64.75

Manual of Outpatient Gynecology edited by Carol Havens, Nancy D. Sullivan & Patti Tilton. Little, Brown and Company, Boston/Toronto, 1986, 282 pages, £10.30

The I.U.D. A Woman's Guide by Robert Snowden. Unwin Paperbacks, London, 1986, 127 pages, £2.75

The Potential of the Traditional Birth Attendant (Who Offset Publication No. 95) edited by A. Mangay Maglacas & John Simons. World Health Organization, Geneva, 1986, 105 pages, Sw Fr 16, US$ 8.00

Ostetricia E Ginecologia Volumes 1 and 2 edited by E. Moracci, E. Martella, N. Ragucci & D. Berlingiere. Idelson, Napoli, 1986, Volume 1, pages 1–822, Volume 2, pages 827–1464 with figures and tables, no price given.

Environmental Health Criteria 59. Principles for Evaluation Health Risks from Chemical during Infancy and Early Childhood: The Need for a Special Approach, World Health Organization, Geneva, 1986, Sw Fr 9

The Book of the Child. Pregnancy to 4 Years Old Second Edition edited by Samuel C. Docherty. Published by the Scottish Health Education Group, Woodburn Lane, Canaan Lane, Edinburgh EH10 4SG, 80 pages fully illustrated with colour plates. Issued free to mothers in early pregnancy

Proceedings and Symposiums

Contributions to Gynecology and Obstetrics. Volume 15. Chorionic Villi Sampling (CVS) International Symposium on First Trimester Fetal Diagnosis, Lausanne, November 1985, edited by G. Pescia & H. Nguyen The. Karger, Basel, 1986, 116 pages, £31.40, DM 96

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution, major changes will be agreed with the author(s)

Presentation of manuscripts

Two copies of the manuscript and illustrations should be sent Manuscripts should be typed double spaced on one side of the paper, with wide margins. The names of author(s) and their appointment(s) and addresses at the time of preparation of the manuscript should be given Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss

Reports of original work should usually be arranged in the conventional order of summary, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part Two further sub-divisions, with appropriately less significant headings, can be used, the third order heading runs on with text at a paragraph opening Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables The summary should contain a factual account of the methods and results in not more than 150 words, rather than a description of the subject of the paper and the opinions of the author(s)

Case reports and short communications do not require a summary or introduction Short communications should not exceed 600 words and contain no more than one table or figure

Tables and figures

Tables and figures should be separate from the text, with their positions indicated in the text margin Both are numbered with arabic numerals Colour illustrations are allowable only in special circumstances and the author will be expected to meet the cost of reproduction

Figures should be marked on the back (light in pencil) with the name(s) of the author(s), the figure number, and the top indicated Each should have a descriptive legend typed on a sheet separate from the figure Photographs should be unmounted glossy bromide prints of good contrast

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc Tables are not included in this classification and should not be submitted as photographs Original X-ray films should not be sent—glossy prints must be submitted

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column)

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself

The identity of patients in illustrations should be concealed by masking the face or eyes, or written permission for publication from the patient or the parent or guardian must be supplied

Units and abbreviations

Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg) If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors Standard abbreviations, without punctuation, are used *Units, Symbols and Abbreviations* (1977) published by the Royal Society of Medicine provides a useful guide Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript Words must appear in full on first appearance in both summary and text, followed by the abbreviation in parenthesis

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text

Statistics

Authors should describe clearly the design of their investigation and the source of the data All statistical methods should be specified so that it is clear which was used where Papers omitting this information may be returned without review The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else

Some points of detail to note are

(1) It is not acceptable to present the results of a statistical analysis solely by a P value—actual results such as means or proportions should always be given, along with the test statistic
(2) The use of confidence intervals is encouraged
(3) The symbol ± should not be used when presenting SE or SD Presentation such as 'the mean   was 14·2 (SD 3 2) mg' is preferred.
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences
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1. Pipril Product Information Book. 2. Limson B.M., *et al.,* Proc. 11th Int. Congr. Chemotherapy, 1979, **1,** 297-299. 3. Prince, A., *et al.*, Proc. 11th ICC and 19th ICAAC, 1979, 295-296. 4. Marlin, G.E., *et al., J. Int. Med. Res.*, 1981, **9,** 268-273. 5. Valenti, S., *et al., Curr. Ther. Res.*, 1983, **33** (5), 745-750. 6. George, C.R.P., and Guinness, M.D.G., *Med. J. Aust.*, 1981, **1,** (1), 36-37. 7. Hoogkamp-Korstanje, J.A.A., *et al., J. Antimicrob. Chemother.* 1981, **8,** 101-106. 8. Viollier, A.F., *et al.*, 2nd Int. Symp. Infec. Immunocom Host 1983, 172-174. 9. Sanders, C.C., *J. Antimicrob. Chemother.*, 1984, **13,** 1-3. 10. Minami, S., *et al., Antimicrob. Ag. Chemother.*, 1980, **18,** (3), 382-385.

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'9, **301,** 677. 2. Richardson,J.A. & Dixon,G., *Brit.Med.J.*, 1976, **1,**
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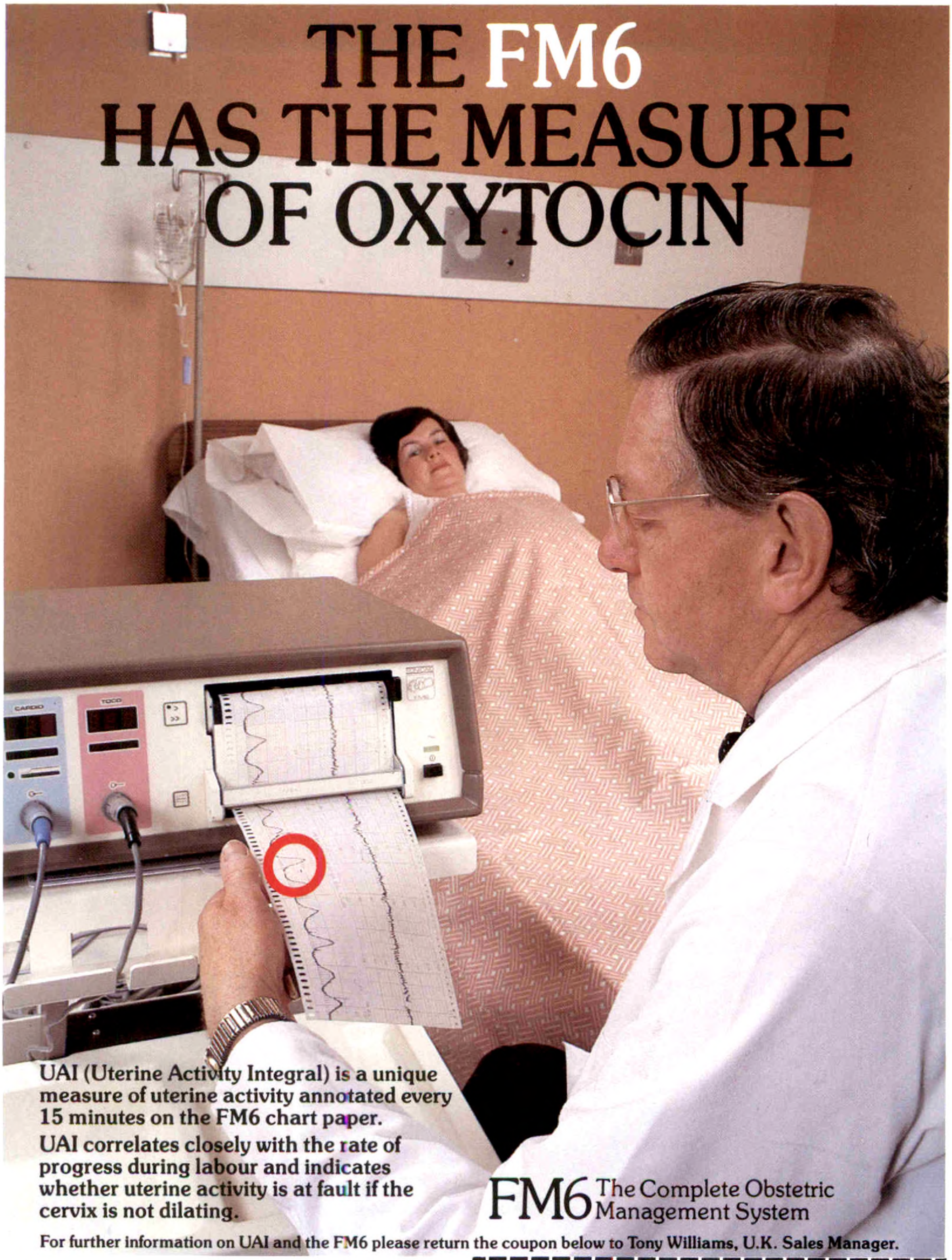

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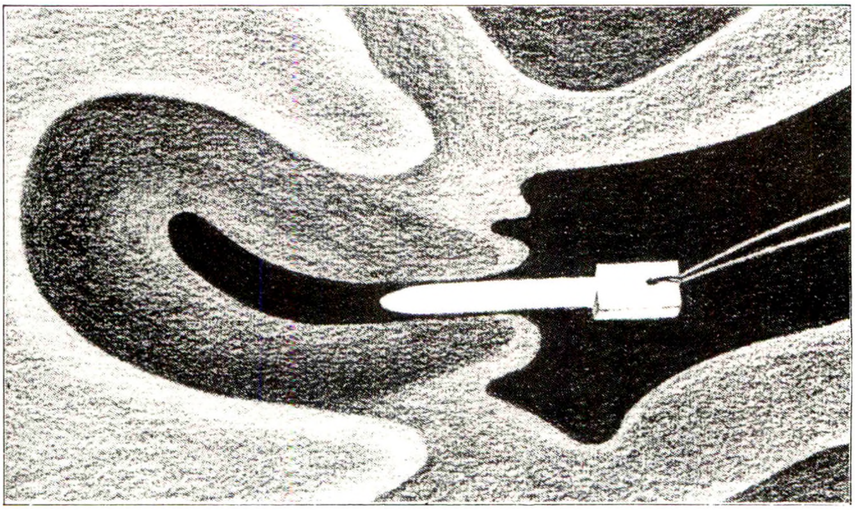

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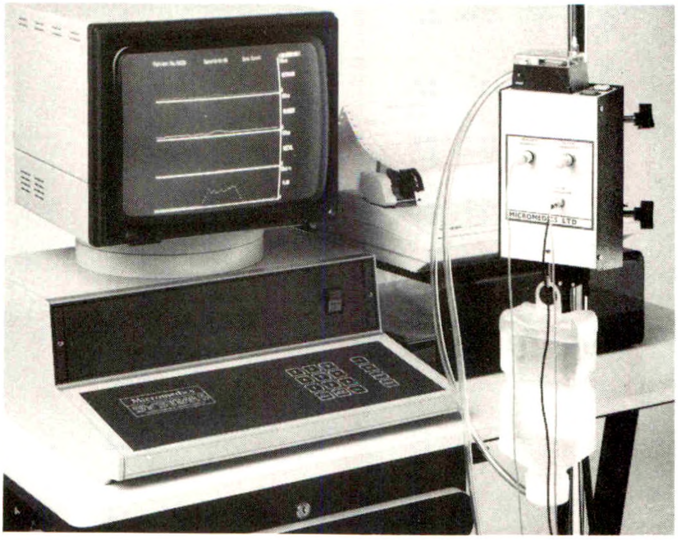

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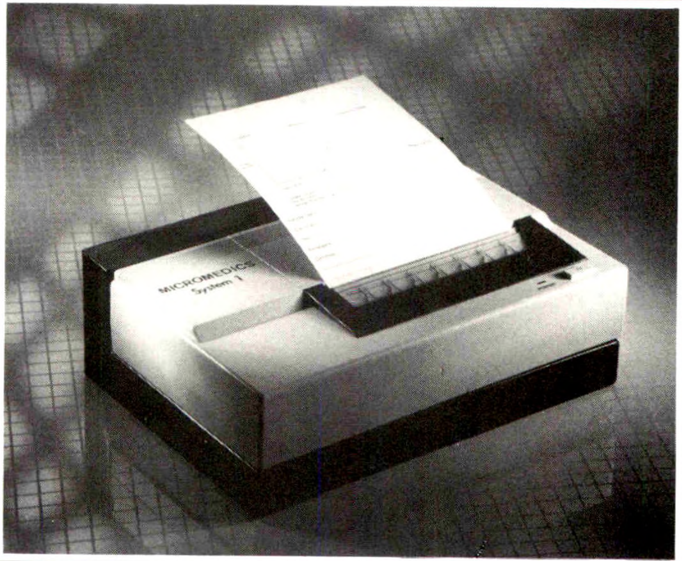

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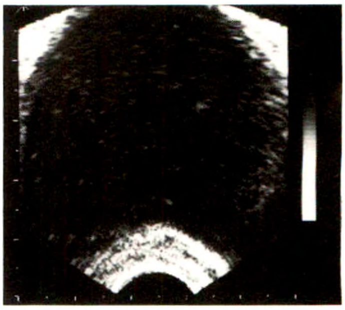

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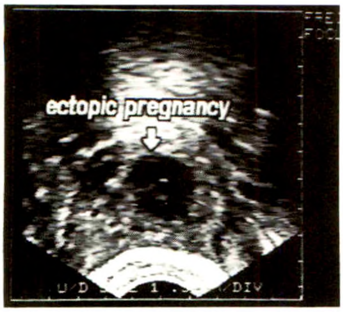

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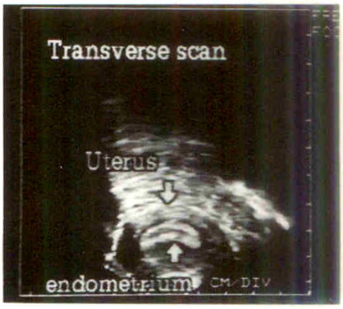

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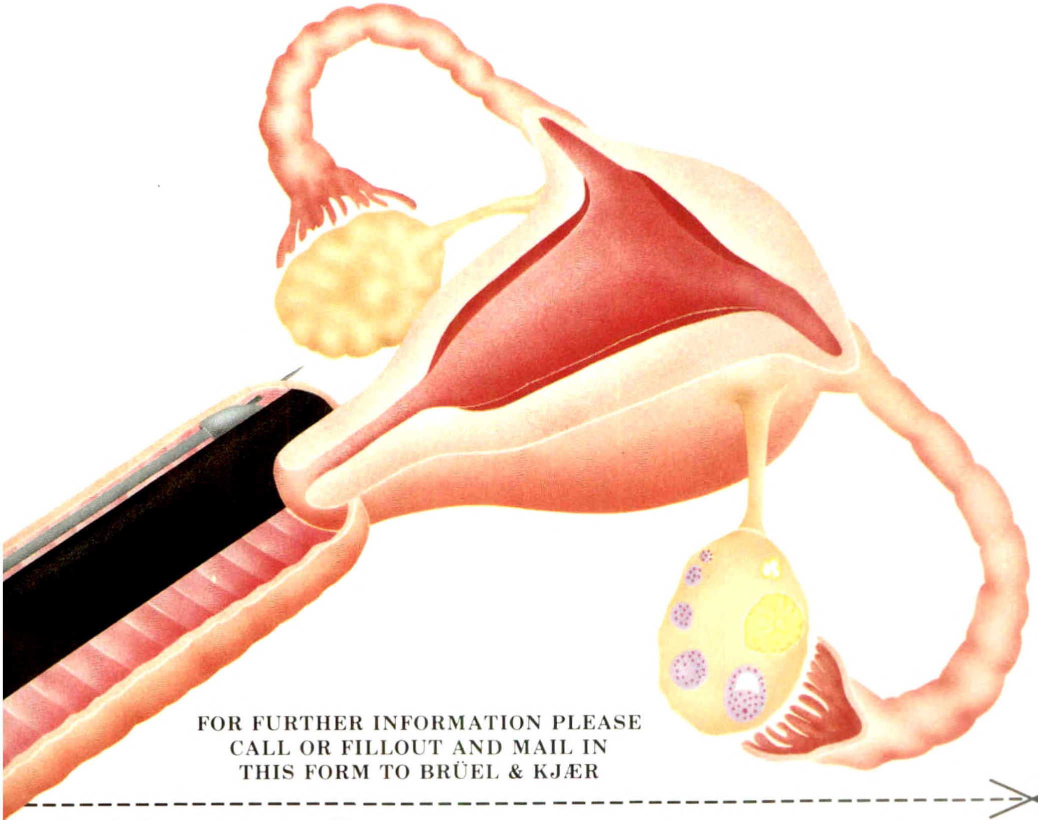

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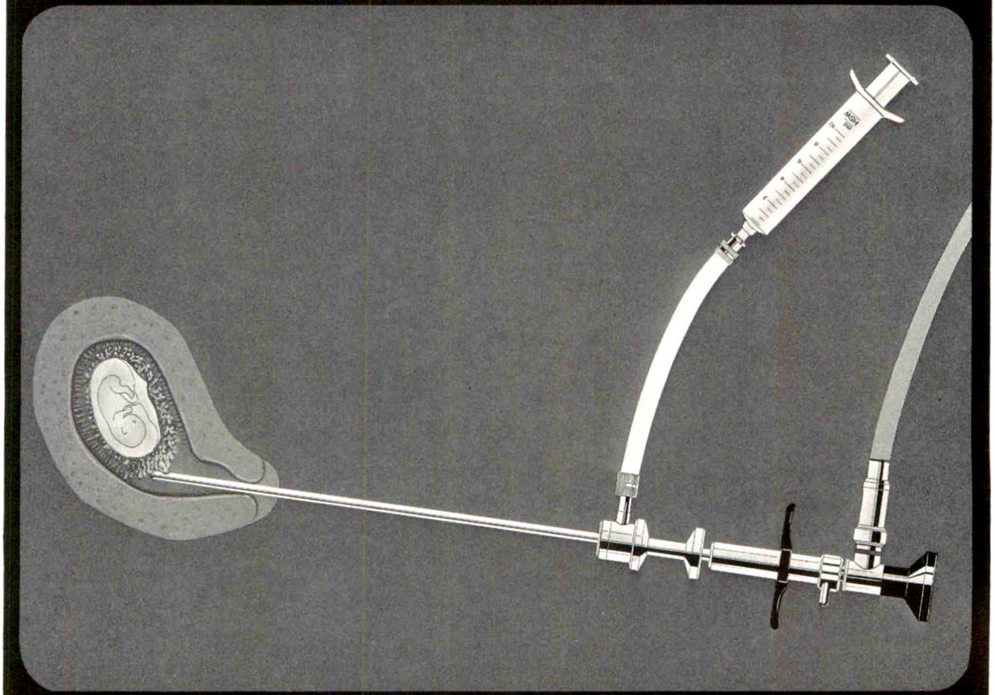

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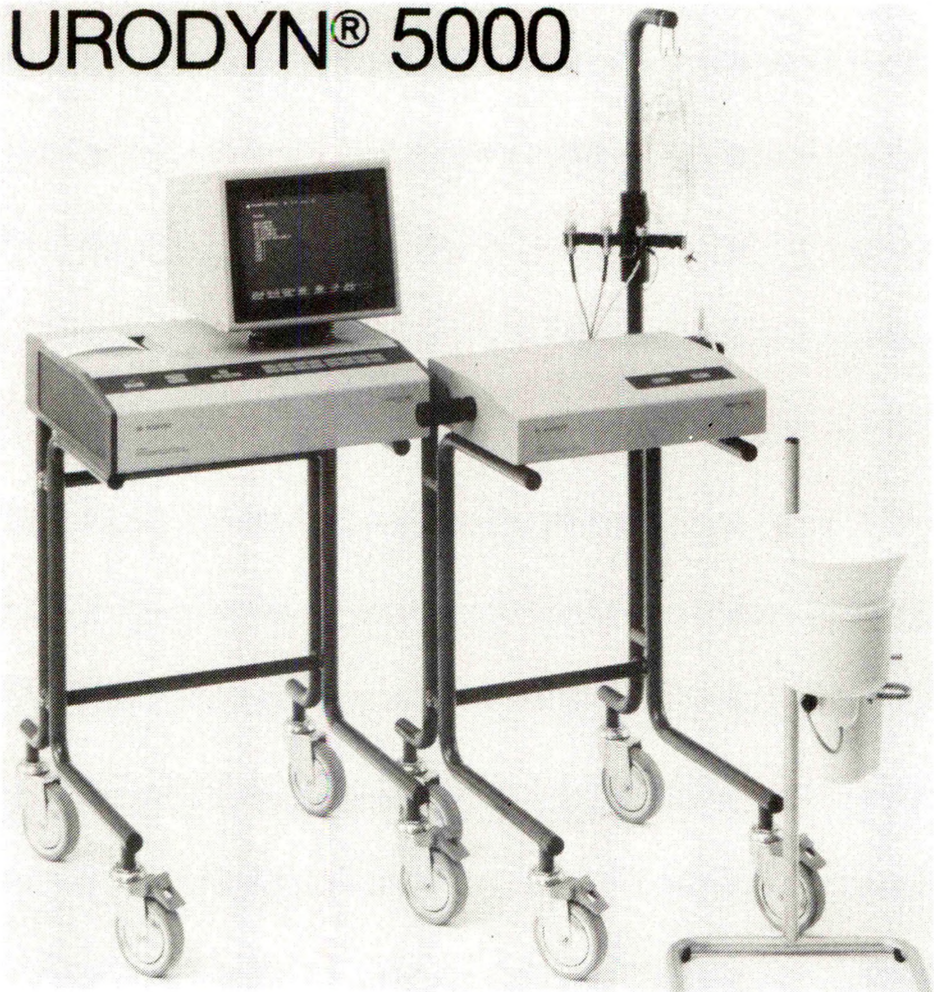

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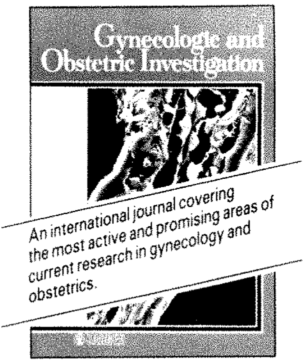

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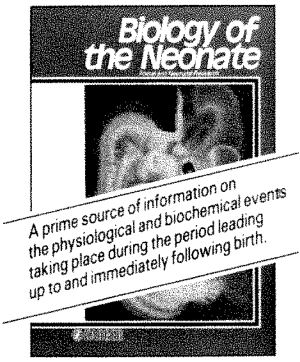

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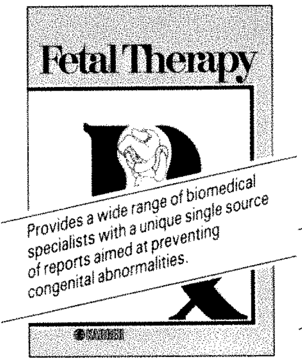

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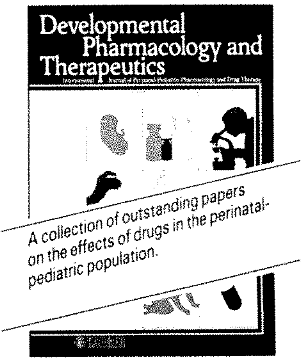

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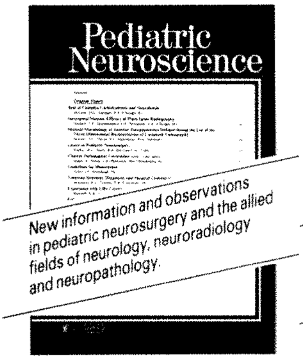

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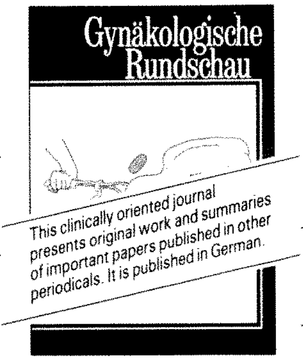

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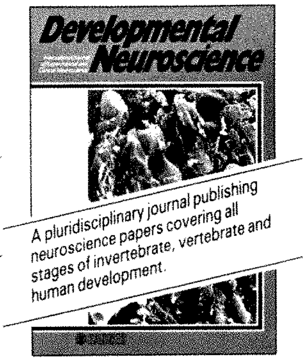

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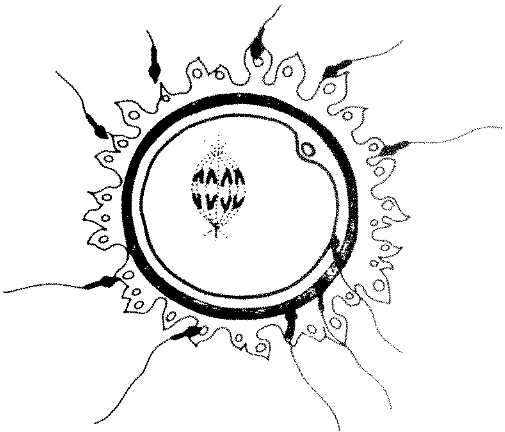

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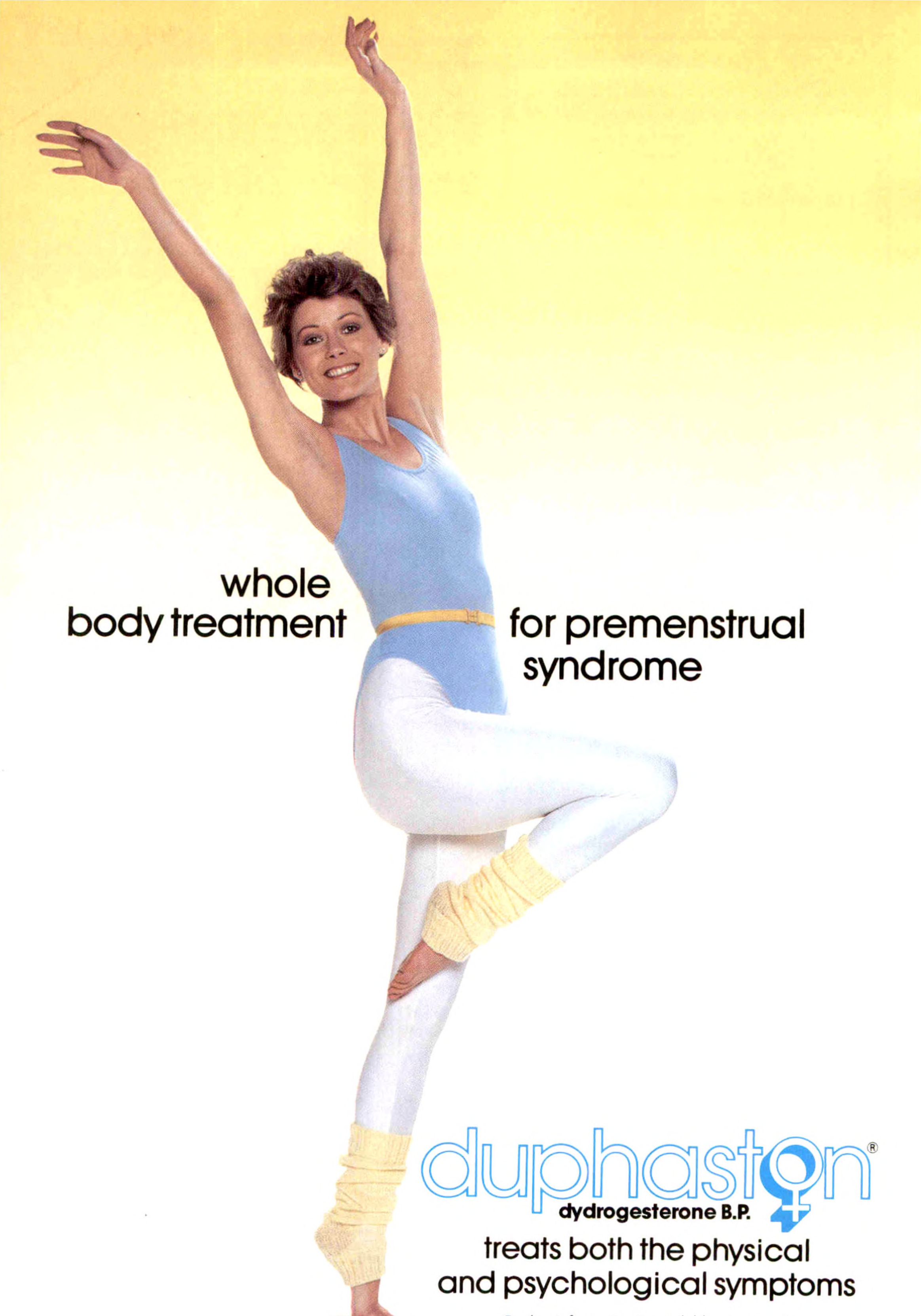

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SIR STANLEY CLAYTON

Stanley Clayton, who edited the Journal from 1963 to 1972, died suddenly on Friday 12th September. It has been the policy since his time that obituaries were no part of the Journal's function, but Stanley Clayton *was* the Journal at an important stage of its development and his going leaves a scar which we cannot ignore. He had high literary standards and hated pretension either in the content or the style of papers. Not everyone warmed to his editorial treatment, although all received a courteous handwritten letter of explanation, but he was unfailingly kind and helpful to the young and inexperienced, and a whole generation in obstetrics and gynaecology benefited from his guidance.

COMMENTARY

Postpartum thyroiditis—an underdiagnosed disease

Most obstetricians would be surprised to learn that up to nearly 9% of their patients could develop thyroid dysfunction in the postpartum period (Nicolai *et al.* 1980; Walfish & Chan 1985). A recent survey in Caerphilly, Wales suggested that the prevalence may be, in fact, much greater than this (R. Hall, personal communication). The diagnosis is often missed because the disorder normally begins after the usual time of the routine postnatal examination. The general practitioner, commonly faced with complaints of tiredness and other non-specific symptoms in the postpartum period, often fails to recognize the possibility of thyroid disease.

Papapetrou & Jackson (1975) described a condition in non-pregnant patients which they called 'painless thyroiditis' or 'hyperthyroiditis' (Jackson 1975). The clinical picture was of a short period of thyrotoxicosis thought to be due to autoimmune destructive processes in the thyroid. Then in Japan, Amino *et al.* (1976) noted the occurrence of transient hypothyroidism 3–6 months postpartum; all of the patients had high titres of antithyroid microsomal antibodies and had evidence of autoimmune thyroiditis.

The attention of endocrinologists then became focused on the thyroid in the postpartum period and in Canada, Ginsberg & Walfish (1977) showed that painless thyroiditis started 1–3 months after delivery with a period of thyrotoxicosis which was often followed after 1–2 months by transient or permanent hypothyroidism (Amino *et al.* 1982*a*; Walfish & Chan 1985). The thyrotoxicosis could be distinguished from that of a postpartum exacerbation of Graves' disease by the finding (in non-breast-feeding women) of a low thyroid uptake of radioactive iodine or technetium. The prevalence of this postpartum transient thyrotoxicosis has been shown to be about 4% in Canada and Japan (Amino *et al.* 1982*a*; Amino & Miyai 1983; Walfish & Chan 1985). The thyrotoxic phase usually starts quite suddenly. The clinical features are not pronounced and indeed fatigue and palpitations are the only two symptoms which are commoner in this group than in normal postpartum control subjects (Amino *et al.* 1982*a*). A goitre is present in just over half the patients and 85% have positive antimicrosomal antibodies (Amino *et al.* 1982*a*). Fine needle biopsy reveals evidence of lymphocytic thyroiditis (Nicolai *et al.* 1980; Inada *et al.* 1981; Jansson *et al.* 1984*a*).

In two thirds of the affected women (Amino *et al.* 1982*a*) the transient thyrotoxicosis goes into remission, the patient becomes euthyroid and remains so. A third of the patients who present in the thyrotoxic phase pass into a hypothyroid phase 4–6 months postpartum (Amino *et al.* 1982*a*).

Some patients with postpartum thyroiditis, perhaps a quarter of the total, appear to go straight into the hypothyroid phase (Amino *et al.* 1982*a*), though it is difficult to be certain that an evanescent phase of thyrotoxicosis has not been missed. About 3·5% of patients with postpartum thyroiditis remain permanently hypothyroid (Amino *et al.* 1982*a*); the rest appear to recover clinically. However, this is a moot point since long-term follow-up of non-pregnant patients with silent thyroiditis shows that about half continue to have a goitre, a third have antimicrosomal antibodies and evidence of a lymphocytic thyroiditis on fine needle biopsy of the thyroid (Nicolai *et al.* 1981). Moreover, raised thyroid stimulating hormone concentrations imply that thyroid reserve is limited and suggest that permanent hypothyroidism may occur in the future (Nicolai *et al.* 1981). These women have a 10–25% risk for attacks of thyroiditis following subsequent pregnancies (Walfish & Chan 1985).

Of the patients who develop postpartum thyroiditis 20–25% have a first-degree relative with autoimmune disease (Farid & Bear 1983). One family has been described in which two sisters and their mother had postpartum thyroiditis (Singer & Gorsky 1985). In Canada Farid *et al.* (1983) found the condition to be associated with HLA DR3 and DR5, though Farid has now withdrawn the DR5 data (R. Hall, personal communication). In those who develop postpartum hypothyroidism and positive microsomal antibodies, a study in Sweden has shown a link with HLA DR4 (Jansson *et al.* 1985). If a patient has an antimicrosomal antibody titre greater than 1/1600 in the first trimester of pregnancy and has given birth to a female baby there is a great chance of her progressing to the hypothyroid phase of thyroiditis in the postpartum period (Amino *et al.* 1982*a*, 1984; Amino & Miyai 1983; Jansson *et al.* 1984*a*).

Why does this disorder occur when it does? It is well recognized that other autoimmune diseases such as myasthenia gravis, rheumatoid arthritis and idiopathic thrombocytopenic purpura may remit during pregnancy but often flare up postpartum (Amino & Miyai 1983). In patients with autoimmune thyroid disease, concentrations of thyroid stimulating antibody (as in Graves' disease) or antimicrosomal antibody (as in thyroiditis) which may be high in the first trimester of pregnancy, decline or even disappear in the middle and last trimesters (Amino & Miyai 1983; Zakarija & McKenzie 1983; Amino *et al.* 1984). Following delivery there is a rebound in the antibodies to high levels (R. Hall, personal communication), resulting in a relapse of Graves' disease or the initiation of thyroiditis (Amino *et al.* 1982*b*, 1984; Amino & Miyai 1983). No generally agreed changes in the T- and B-lymphocytes of the immune system, either during pregnancy, or following it have been shown in the patients who go on to develop thyroiditis, nor are there any specific changes in the T- or B-cells in either the thyrotoxic or hypothyroid phases of that condition (Walfish & Chan 1985). But, Jansson *et al.* (1984*b*) have shown, on fine needle biopsy of the thyroid, that there is an increase in B-lymphocytes and a decrease in suppressor cytotoxic T-cells, findings similar to observations they had previously made in patients with Hashimoto's thyroiditis (Jansson *et al.* 1983).

Treatment of the patient in the thyrotoxic phase of postpartum thyroiditis is problematical since the use of antithyroid drugs is inappropriate, the thyrotoxicosis being due to the excessive release of thyroid hormone caused by destruction of the gland, rather than to the excessive production of thyroid hormone. Antithyroid agents such as carbimazole or propylthiouracil in this situation are likely to accelerate the progress to hypothyroidism by inhibiting thyroid hormone synthesis. If the patient's symptoms are sufficiently severe, a beta-adrenergic receptor blocking agent such as propranolol can be used to reduce the severity of palpitations, sweating, tremor, etc. It is, however, important to remember when interpreting thyroid function tests in these patients that propranolol raises total and free thyroxine (T_4) levels and reduces total and free triiodothyronine (T_3) concentrations because it tends to inhibit the conversion of T_4 to T_3 (Kristensen & Weeke 1977; Cooper *et al.* 1982; Perrild *et al.* 1983).

Once the thyrotoxic phase is over the propranolol should be stopped, but the patient should be followed up monthly to see whether or not she becomes hypothyroid. Here the appropriate investigations are total or free T_4 and thyroid stimulating hormone (TSH) levels, the former two being reduced and the latter increased during the hypothyroid phase. If the hypothyroidism is mild it may be possible to leave it untreated, in the expectation that the condition will resolve spontaneously. If, on the other hand, symptoms are severe, it is justified to prescribe replacement thyroxine. After 6 months of treatment the patient should have the thyroxine stopped, because in the majority of patients the disease will have gone into remission (Walfish & Chan 1985). Thyroid function tests are done a month or so later to make sure that this has happened.

The lessons to be learned by the obstetrician from the research work done on postpartum thyroiditis over the last 10 years are that any woman who has a previous history of autoimmune thyroid disease or who has a first degree relative with it, should have her thyroid antimicrosomal antibodies measured during the first trimester of pregnancy. If they are present, a free T_4 and TSH should be measured to make sure that she is euthyroid during pregnancy and she should be monitored carefully for thyroiditis during the postpartum period.

Ian Ramsay
Consultant Endocrinologist
North Middlesex Hospital,
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The effects of inflammatory bowel disease on pregnancy: a case-controlled retrospective analysis

R. J. PORTER, G. M. STIRRAT

Summary. Retrospective analysis of 82 pregnancies in women with either ulcerative colitis or Crohn's disease suggested that, in general, neither disease had a major effect on pregnancy outcome. The birthweights of babies born to women with inflammatory bowel disease were marginally lower than those born to women in a control group matched for age and parity, but the difference was statistically significant only in women with Crohn's disease. In both disease groups there was a higher frequency of low haemoglobin levels in pregnancy than in the matched control groups. There were no statistically significant effects of ulcerative colitis or Crohn's disease on duration of pregnancy, mode of delivery or raised blood pressure and/or proteinuria. In the absence of a relapse, a diagnosis of inflammatory bowel disease should not influence obstetric management.

Several aspects of the effects of inflammatory bowel disease on pregnancy and fertility, and the effects of pregnancy on the disease have been studied, but only very broad measures of obstetric outcome have been considered, and there have been no case-control studies. Overall, the rate of spontaneous abortion and the prospects for a live birth are no different in patients with inflammatory bowel disease than in the general population (Homan & Thorbjarnarson 1976; Willoughby & Truelove 1980). However, if the disease is active at the time of conception, and particularly if there is further deterioration, Nielsen *et al.* (1983, 1984) reported that spontaneous abortion was more likely. Some reports suggest that deterioration in disease state, particularly if surgery is required, or onset of disease during pregnancy, adversely affects fetal outcome (de Dombal *et al.* 1965, 1972; McEwan 1973; Martimbeau *et al.* 1975), but this is contradicted in other studies (Nielsen *et al.* 1983, 1984). Beyond these, few definitive statements can be made. We report the results of a retrospective case-control analysis of 82 pregnancies in patients with inflammatory bowel disease. We have considered the effects of the disease on birthweight, duration of pregnancy, mode of delivery, lowest maternal haemoglobin level recorded in pregnancy, and the incidence of raised blood pressure and/or proteinuria in pregnancy.

Patients and methods

Data for the index cases were retrieved from the Oxford Recording Linkage Survey. They represent the experience of the John Radcliffe Hospital, Oxford over 10 years (1972–1981). The diagnoses of either ulcerative colitis or Crohn's disease had been established by the appropriate gastro-enterological criteria. Only pregnancies which progressed beyond 24 weeks were included.

For each case two control subjects matched for maternal age at delivery, parity and gravidity were found. The control subjects were selected

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from the labour ward register by finding those deliveries immediately before and immediately after each index case where matching was complete. Exact matching for all three variables was possible in 85% of the controls. For some of the older multigravid index cases exact matching proved impossible (within 6 months of the delivery date) so that 13% of the controls were matched exactly for parity and gravidity but only to within 2 years for maternal age. Three controls were matched for age and parity but not for gravidity, the three relevant index cases were para 2 gravida 6, para 4 gravida 7, and para 1 gravida 5.

Gestational age at delivery was derived from maternal menstrual dates, supplemented where appropriate by first or early second trimester ultrasound scan data. Where there was considerable uncertainty, neonatal paediatric assessment was also used.

The birthweight centile nomograms of Altman & Coles (1980) were used, both with and without correction for maternal weight and height at 20 weeks gestation.

Chi squared tests, and where appropriate Fisher's exact test, were used to assess significance of differences between the index cases and their control groups.

Ulcerative colitis cases

There were 44 deliveries in 38 patients with ulcerative colitis. Maternal age varied from 20 to 40 years, and parity from para 0+0 to para 4+1. Fifty per cent of the pregnancies were in nulliparous women (Table 1).

In 18 cases the women did not require medication for their disease at the time of conception; four of the 18 had had total colectomies and ileostomies. In one patient the disease was diagnosed only in the puerperium. In nine of these 18 cases (50%) the disease worsened during the pregnancy, including two pregnancies where the disease was recognized for the first time in the second trimester, but four of the nine did not require medication.

Of the remaining 26 cases, 23 (88%) were taking sulphasalazine (alone, or in combination with other medications) at the outset of the pregnancy. The other three were taking codeine phosphate and/or prednisolone enemas as required symptomatically. (One of the three had had total colectomy and ileostomy). There was a worsening of the disease symptoms during eight pregnancies and in one case in the puerperium (35%), and five of these required additional medication.

Overall, therefore, there was a symptomatic deterioration in 18 cases (41%), but in no case was surgery required in the pregnancy or the puerperium.

The mean birthweight centiles did not differ significantly between the cases and controls ($P>0{\cdot}1$, Table 2), and the frequency of low birthweight babies (<10th centile) was similar in both groups, whether correction was made for

Table 1. Characteristics of 44 pregnancies in 38 patients with ulcerative colitis cases

Variable	No (%)	
Age (years)		
≤20	1 (2)	
21–25	4 (9)	
26–30	23 (52)	
31–35	10 (23)	
36+	6 (14)	
Parity		
0	22 (50)	
1	15 (34)	
2	4 (9)	
3+	3 (7)	
	Symptomatic deterioration	Medication altered
Previous ileostomy ($n = 5$)	1	1
Medication at pregnancy outset		
Nil ($n = 18$)	9	5
Sulphasalazine alone ($n = 17$)	5	4
Sulphasalazine + other medication ($n = 6$)	2	0
Steroids and/or codeine phosphate ($n = 3$)	2	2

Table 2. Clinical characteristics of 44 pregnancies in women with ulcerative colitis (UC) compared with a control group

Variable	Cases ($n = 44$)	Controls ($n = 88$)
Maternal mid-pregnancy weight (kg)		
mean (SEM)	63·4 (1·7)	61·5 (1·1)
Birthweight centile		
mean (SEM)		
Uncorrected for maternal weight and height		
No deterioration in UC during pregnancy ($n = 27$)	47·3 (5·6)	
Deterioration in UC during pregnancy ($n = 17$)	53·2 (6·1)	
Total ($n = 44$)	50·4 (4·0)	54·4 (3·0)
Corrected for maternal weight and height		
No deterioration in UC during pregnancy ($n = 27$)	43·0 (5·2)	
Deterioration in UC during pregnancy ($n = 17$)	48·5 (5·7)	
Total ($n = 44$)	45·1 (3·9)	51·4 (2·9)
Gestational age at onset of labour		
≥37 weeks		
Spontaneous	25 (57%)	44 (50%)
Induced or elective CS	12 (27%)	38 (43%)
Total	37 (84%)	82 (93%)
<37 weeks		
Spontaneous	4 (9%)	5 (6%)
Induced or elective CS	3 (7%)	1 (1%)
Total	7 (16%)	6 (7%)
Mode of delivery		
Spontaneous vaginal	24 (55%)	45 (51%)
Forceps		
Non-rotational	11 (25%)	26 (30%)
Rotational	2 (5%)	10 (11%)
Total	13 (30%)	36 (41%)
CS		
Emergency	4 (9%)	5 (6%)
Elective	3 (7%)	2 (2%)
Total	7 (16%)	7 (8%)
Pregnancy complications		
Raised diastolic blood pressure (>90 mmHg)	6 (14%)	15 (17%)
Proteinuria	1 (2%)	4 (5%)
Low haemoglobin (<10·5 g/dl)	9 (20%)	3 (3%)*

CS, Caesarean section.

* Significant difference between the cases and controls ($P<0{\cdot}005$).

maternal weight or not (Fig. 1). Maternal weights did not differ significantly between the two groups (Table 2). Furthermore there was no difference in the birthweight distribution between those in whom the disease had remained stable and those in whom symptoms had worsened during the pregnancy or puerperium.

Although premature delivery (before 37 completed weeks gestation) was more common in the index cases than in the controls, the difference was not significant. Premature deliveries occurred with equal frequency in pregnancies during which the disease deteriorated as in those where there was no such change. There were no differences in modes of delivery or frequency of pregnancy complications (e.g. hypertension) between the cases and the controls.

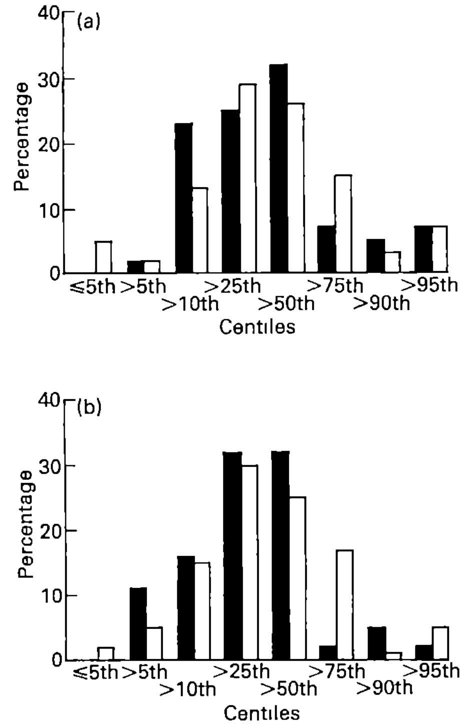

Fig. 1. Distributions of birthweight centiles (a) uncorrected and (b) corrected for maternal height and weight in women with ulcerative colitis (■) and their control subjects (□). (There were no significant differences in the distributions between the two groups).

Low haemoglobin levels (<10·5 g/dl) were found more frequently ($P<0{\cdot}005$) in the index cases (9 of 44) than in the controls (3 of 88). Six of those with low haemoglobin levels were among the group of 18 pregnancies during which the disease state worsened (3%, compared with 12% of those where the disease remained stable: this was not significant).

Because patients who have had a total colectomy and ileostomy could be regarded as a totally different sub-group, the data were analysed again after excluding the five patients who had had surgery. However, the results were unchanged except that the significance of the difference between the cases and controls for frequency of low maternal haemoglobin was greater ($P<0{\cdot}001$).

There were no perinatal deaths among the index cases. One infant was hypospadiac but no other congenital abnormalities were reported in the neonatal period.

Crohn's disease cases

There were 38 deliveries in 30 patients with Crohn's disease, maternal age varied from 17 to 41 years, and parity from para 0+0 to para 4+2. Fifty-three per cent of the pregnancies were in nulliparous women (Table 3).

In 19 cases the women required no medication for their disease at conception. Of these, seven had had major surgery (e.g. hemicolectomy). In

Table 3. Characteristics of 38 pregnancies in 30 patients with Crohn's disease

Variable	No. (%)	
Age (years)		
≤20	4 (11)	
21–25	8 (21)	
26–30	19 (50)	
31–35	4 (11)	
36+	3 (8)	
Parity		
0	20 (53)	
1	9 (24)	
2	4 (11)	
3+	5 (13)	
	Symptomatic deterioration	Medication altered
Previous major bowel resection (*n* = 14)	2	0
Medication at pregnancy outset		
Nil (*n* = 19)	2	1
Sulphasalazine alone (*n* = 7)	2	1
Sulphasalazine + other medication (*n* = 8)	2	1
Steroids and/or codeine phosphate (*n* = 4)	1	1

two of these cases the disease worsened during the pregnancy, but only one required treatment, which involved admission to hospital and surgery in the first post-natal week after delivery (Table 3).

In the remaining 19 cases, 15 (79%) were taking sulphasalazine (alone or in combination with other medications) at the beginning of the pregnancy and four were taking codeine phosphate and/or steroids (in oral or enema form). The disease deteriorated during five pregnancies, necessitating increased medication in three and admission to hospital in one.

Overall therefore there was a deterioration of the disease in seven cases (18%).

There was a significant increase in low birthweight infants (<10th centile) in the index cases compared with the controls (Fig. 2a), but only if birthweights were not corrected for maternal weight and height at mid-pregnancy ($P = 0{\cdot}046$). If such correction is made (Fig. 2b), the difference becomes less striking ($P = 0{\cdot}052$). There were no significant differences between the cases and controls, for mean birthweight centiles, whether corrected or uncorrected weights were used, nor for maternal weights (Table 4). In only one of the six pregnancies associated with low birthweight babies (<10th centile) had there been a deterioration of the disease during the pregnancy, indeed the infant with nearly the lowest birthweight centile was born to a patient whose disease had improved sufficiently to reduce medication during the pregnancy. In four of the six cases the disease was active and/or requiring maintenance medication at the start of the pregnancy, but this association was not statistically significant. There was no significant difference in mean birthweight centiles between the women who had had previous bowel resection for Crohn's disease and those who had not (Table 4).

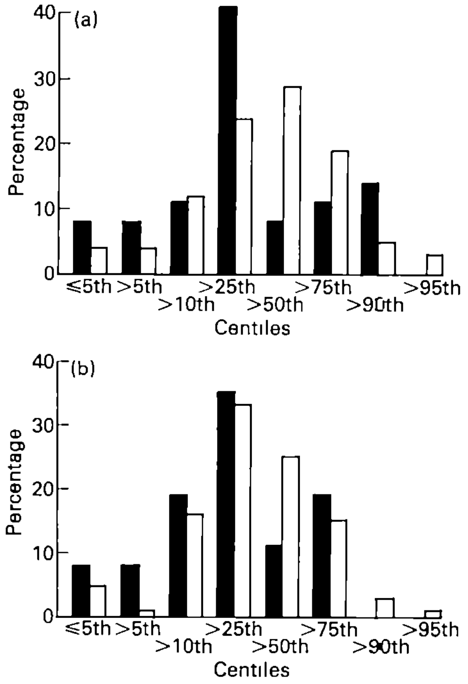

Fig. 2. Distributions of birthweight centiles (a) uncorrected and (b) corrected for maternal height and weight in women with Crohn's disease (■) and their control subjects (□) (Distributions of numbers below the 10th centile and those above the 50th centile are significantly different between the two groups for (a) ($P = 0{\cdot}046$) but not for (b) ($P = 0{\cdot}052$).

Premature delivery (before 37 completed weeks) was more common, but not significantly so, in the cases than in the controls. Only one of the six premature deliveries occurred in a woman who had had previous bowel resection for Crohn's disease. No difference was observed in modes of delivery or rate of pregnancy complications (e.g. hypertension) between the cases and the controls.

Induced delivery (either by induction of labour or by elective caesarean section) occurred much more often in the index cases than in the controls (Table 4). In four of the 22 induced deliveries Crohn's disease was cited as the indication to expedite delivery and in four others the disease was indirectly implicated. This contrasts with the findings in patients with ulcerative colitis.

Low haemoglobin levels (<10·5 g/dl) occurred significantly more often in the index cases than in the controls ($P < 0{\cdot}05$). Four of the six cases occurred among the seven pregnancies during which the disease deteriorated, this was a significant association ($P < 0{\cdot}005$).

There was one intrauterine fetal death, in a patient who required oral prednisolone throughout the pregnancy for her disease which responded incompletely. There were no reports of congenital abnormalities among the infants of index cases. There was also a maternal death directly attributable to Crohn's disease; the patient suffered a serious relapse of her disease in the third trimester and had a spontaneous premature labour. Bowel resection was per-

Table 4. Clinical characteristics of 38 pregnancies in women with Crohn's disease compared with a control group

Variable	Cases ($n = 38$)	Controls ($n = 76$)
Maternal mid-pregnancy weight (kg)		
mean (SEM)	61·6 (2 4)	62·2 (1·0)
Birthweight centile mean (SEM)		
Uncorrected for maternal weight and height		
Previous bowel resection ($n = 14$)	46·3 (8·4)	
No previous bowel resection ($n = 23$) (one twin pregnancy excluded)	44·3 (5·7)	
Total ($n = 37$)	45·1 (5·1)	52·9 (3·2)
Corrected for maternal weight and height		
Previous bowel resection ($n = 14$)	41·7 (7·4)	
No previous bowel resection ($n = 23$)	38·5 (5·7)	
Total ($n = 37$)	39·8 (4·5)	47·2 (3·1)
Gestational at and onset of labour		
≥37 weeks		
Spontaneous	12 (32%)	47 (62%)
Induced or elective CS	20 (53%)	23 (30%)*
Total	32 (84%)	70 (92%)
<37 weeks		
Spontaneous	4 (11%)	4 (5%)
Induced or elective CS	2 (5%)	2 (3%)
Total	6 (16%)	6 (8%)
Mode of delivery		
Spontaneous vaginal	18 (47%)	46 (61%)
Forceps		
Non-rotational	6 (16%)	19 (25%)
Rotational	4 (11%)	2 (3%)
Total	10 (26%)	21 (28%)
CS		
Emergency	7 (18%)	7 (9%)
Elective	3 (8%)	2 (3%)
Total	10 (26%)	10 (13%)
Pregnancy complications		
Raised diastolic blood pressure (>90 mmHg)	5 (13%)	12 (16%)
Proteinuria	2 (5%)	3 (4%)
Low haemoglobin (<10·5 g/dl)	6 (16%)	3 (4%)*

CS, Caesarean section.

* Significant differences between the cases and controls: $P<0{\cdot}0001$ for induction of labour (including elective CS) and $P<0{\cdot}05$ for low haemoglobin.

premature labour. Bowel resection was performed in the first week after delivery and she died as a result of a massive pulmonary embolus 5 days later.

Discussion

The striking feature revealed by this study is how relatively little effect inflammatory bowel disease has on pregnancy. This has been suggested before (de Dombal *et al.* 1965, 1972; Willoughby & Truelove 1980; Mogadam *et al.* 1981; Nielsen *et al.* 1983, 1984), but we are able to confirm it with precision.

That being said, it is of note that Crohn's disease had a (previously unrecognized) deleterious effect on birthweight, not related to any effect that the disease may have had on maternal weight. There were too few pregnancies associated with a deterioration of the disease to ascribe the effect on birthweight to this factor, in fact there were more (4 vs 2) small-for-dates infants among those that did not deteriorate, and there was no significant association with the use of medication during the pregnancy. We conclude therefore that low birthweight for gestation should be considered a risk in all pregnancies in patients with Crohn's disease, whatever the state of the disease at the outset, whether the disease deteriorates during the pregnancy or not, and irrespective of the medication required. This conclusion is at variance with that made by Mogadam *et al.* (1981), but their paper referred to low birthweight (<2500 g) with no consideration of gestational age, and compared index cases with the general population, so that their conclusions about pregnancy outcome are not comparable to ours.

There was a trend towards lower birthweight in babies born to women with ulcerative colitis compared with their controls. But even though there were more women with ulcerative colitis than with Crohn's disease this trend was not statistically significant, irrespective of the disease state in the pregnancy; we therefore conclude that it does not represent a real problem in clinical practice.

The finding that inflammatory bowel disease had no effect on modes of delivery, pregnancy complications or gross fetal or neonatal morbidity, is reassuring.

Although not statistically significant, there were more premature deliveries in both disease groups than their respective control groups. Nielsen *et al.* (1984) found this to be significant for Crohn's disease, but not for ulcerative colitis (Nielsen 1983). The difference between these results and ours may be due solely to the larger sample sizes in their studies.

It is perhaps not surprising that there should be a higher frequency of low haemoglobin levels during pregnancy in women with inflammatory bowel disease than in the control groups, given the propensity to overt or occult gastro-intestinal bleeding. It would be impossible to compute whether selective administration of haematinics had confounded the validity of this finding, but it seems inherently unlikely that these should have been witheld preferentially from index cases and given to the controls—if anything, one might suspect the opposite. It may be, however, that the patients with disease were less likely to comply with such medication because of gastro-intestinal side-effects. Whatever the cause, it appears that a low haemoglobin level is more common during pregnancies associated with inflammatory bowel disease, and regular checks to exclude this may be advisable.

The strikingly higher rate of induced delivery in pregnancies with Crohn's disease than either in those with ulcerative colitis or in the control group, even when considered in the perspective of the high overall induction rate at this hospital during the study period, suggests that thresholds for concern are already lowered in pregnancies associated with Crohn's disease. We consider that this is appropriate, but that the areas of obstetric, as distinct from gastro-enterological, concern are specific, as shown above, and do not indicate alteration of the normal management of pregnancy.

Previous studies have emphasized the dangers of marked deterioration in, or poor control of, inflammatory bowel disease in pregnancy, particularly if surgery is required (Martimbeau *et al.* 1974; McEwan 1973; Korelitz 1983). This study includes one fetal and one maternal death, both of which occurred under just these circumstances. Such cases are fortunately uncommon, certainly less so than reported in earlier studies, and should not deflect from the otherwise optimistic picture of the effects of inflammatory bowel disease on pregnancy. Nor should it be surprising that such major intra-abdominal pathology can, in its fulminating form, have such devastating fetal and maternal consequences.

This study was not intended to consider the effect of pregnancy on inflammatory bowel disease. Such studies are complicated by the heterogeneity of the populations studied, in terms of site of disease, severity of disease at onset of pregnancy, type and dosage of medications (if any), type and extent of previous surgery (if any), and require large numbers to achieve valid conclusions. In the present study, the frequencies of symptomatic deterioration in both disease groups during pregnancy are broadly in line with those observed by other workers, and are compatible with the proposition that deterioration is no commoner during a pregnancy than in the non-pregnant state (Nielsen *et al.* 1983, 1984).

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Fetal and maternal effects of forceps and vacuum extraction

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Summary. Between 1976 and 1984, 223 forceps deliveries were compared with the next vacuum extraction that occurred in the labour ward. The groups did not differ in gestational age, parity, presentation and station of fetal head at start of the delivery, infant birthweights, or the indication for the procedure. Of the forceps deliveries, 66% were performed by a specialist, compared with only 16% of the vacuum extractions. Maternal complications were equally common in both groups. Severe birth canal trauma occurred in 7% of each group. Low 1-min Apgar scores (<7) were found significantly ($P<0{\cdot}01$) more often in the vacuum extraction group (36 infants) than in the forceps group (17 infants).Cephalohaematomas and scalp lesions, neonatal jaundice and clavicular fracture were all significantly less common after forceps than after vacuum extraction. One infant in the vacuum group had a cranial fracture.

In some studies, almost identical fetal complications have been found after delivery by forceps as after vacuum extraction (Schenker & Seer 1967), and there were no differences in neonatal acid-base balance (Livnat *et al.* 1978). Most comparative studies, however, have suggested the advantages of vacuum extraction for both the infant and the mother (Sjöstedt 1967; Chiswick & James 1979; Greis *et al.* 1981). In a recent follow-up study of adults who were born either by forceps or vacuum extraction, paradoxically, those born by forceps has a significantly higher mean intelligence quotient than those born by vacuum extraction and also higher than the national average (Nilsen 1984).

In the present study we report our findings of the effects of forceps and vacuum extraction on the mother and the newborn.

Subjects and methods

The study included all 223 forceps deliveries performed at the department of obstetrics and gynaecology of Tampere University Central Hospital in the 9 years 1976–1984. Of these, 178 (80%) were in nulliparae. The gestation at delivery was between 37 and 41 weeks in 190, < 36 weeks in 17 and ≥ 42 weeks in 16 patients. Marked immaturity has been considered as a contraindication for forceps delivery. The women who had a forceps delivery were compared with 223 women who had a vacuum extraction during the same period. The next vacuum delivery after each forceps delivery was chosen for the comparison group. Of the vacuum extraction patients 189 (85%) were nulliparae and the gestation was 37–41 weeks in 193 (87%), < 36 weeks in 8 (4%) and ≥ 42 weeks in 22 (10%). The Malmström type of vacuum extraction was used exclusively and the forceps were Wichmann and Zeppelin. General anaesthesia was not used for any of the deliveries.

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The indications for forceps delivery were fetal distress in 84 (38%), protracted labour in 123 (55%) and others in 16 patients. The corresponding numbers in the vacuum extraction group were 86 (39%), 119 (53%) and 18 (8%), respectively.

The presentation and the station of the fetal head at the start of the delivery did not differ significantly between the two study groups (Table 1). Of the forceps deliveries 148 (66%) were performed by a specialist and 75 (34%) by a doctor in training. In the vacuum extraction group the corresponding figures were 35 (16%), and 188 (84%).

Maternal morbidity was analysed in terms of vaginal and cervical lacerations, amount of bleeding, fever (at least 2 days > 38°C) duration of hospital stay.

The infants were examined by a paediatrician. Neonatal morbidity was assessed in terms of Apgar scores, cephalhaematomas and scalp lesions, jaundice, and other evidence of trauma, including intracranial haemorrhage, signs of cerebral irritation, and mortality.

Statistical analysis used the χ^2 test.

Results

Maternal complications

Severe birth canal injury (third and fourth degree tears) were relatively uncommon in both study groups. The occurrence of severe injury and of smaller cervical and vaginal lacerations was the same in the forceps and vacuum extraction groups. There were also no statistical differences in the amount of bleeding, fever, or duration of the hospital stay between the study groups (Table 2).

Table 1. Presentation and station of the fetal head at the start of extraction

Characteristic	Forceps delivery (n=223)	Vacuum extraction (n=223)
Presentation		
Normal	186	172
Occiput posterior	35	40
Deep transverse arrest	2	11
Station		
≤0	6	18
+1, +2	63	78
+3, +4	154	127

Neonatal complications

The birthweights of the infants did not differ significantly between the two groups (Table 3). Low 1-min Apgar scores (< 7) were seen in 17 infants in the forceps group and in 36 in the vacuum extraction group; a statistically significant difference ($P<0{\cdot}01$). The 5-min Apgar scores were similar in the two groups (Table 3).

Cephalhaematomas and scalp lesions were significantly more common after vacuum extraction ($P<0{\cdot}001$), as was neonatal jaundice ($P<0{\cdot}05$), and clavicular fracture ($P<0{\cdot}05$). Other neonatal complications were rare in both groups and did not differ significantly (Table 2).

Cerebral haemorrhage was diagnosed in two surviving infants born by vacuum extraction but in none in the forceps group. Three infants died in the vacuum extraction group: two of sepsis and one of congenital cerebral atrophy. One infant in the forceps group died due to the meconium aspiration syndrome.

The vacuum extractor came off unexpectedly during 42 deliveries, 36 (86%) of these were in nulliparae. Of these 42 infants, 27 were born after reapplication of the vacuum extractor and the other 15 by forceps. Eight of the 27 infants born by vacuum extraction (19%) and three of the 15 born by forceps had Apgar scores of <7. Four of these infants born by vacuum extraction had clavicular fracture compared with none in the forceps group. One infant had a cranial fracture and in this case the vacuum extractor came off three times.

Discussion

In Finland during the 1960s, as in several other European countries, vacuum extraction virtually replaced forceps. Forceps were considered traumatic and dangerous for both the infant and the mother. Since the mid-1970s, however, the practice in our hospital has changed. Forceps delivery has come back and its use has gradually increased.

Studies comparing forceps and vacuum extraction usually show that vacuum extraction is more advantageous for both infant and mother (Sjostedt 1967; Greis *et al.* 1981). Sometimes the groups compared have been from different time periods (Schenker & Serr 1967). Practices in different departments have also been compared (Lange 1964). The indications for the procedures have been different and fetal distress has

Table 2. Maternal and neonatal morbidity in forceps and vacuum extraction deliveries

Morbidity	Forceps delivery (n=223)	Vacuum extraction (n=223)
Maternal		
Severe birth canal trauma	7	7
Cervical and vaginal lacerations	69	69
Bleeding (> 500 ml)	11	19
Fever (> 38°C)	4	9
Hospital stay (≥8 days)	29	36
Neonatal		
Cephalhaematoma, scalp lesion	40	81
Neonatal jaundice	52	71
Fractured clavicle	12	24
Signs of cerebral irritation	6	5
Erb's palsy	0	2
Anaemia	0	1
Cranial fracture	0	1
Neonatal death	1	3

tended to be a more common indication in the forceps group. In the present study, fetal distress and protracted labour were equally common in both groups. Neither the presentation and station of the fetal head at the start of extraction, nor the length of the second stage of labour, differed between the two groups. However, 66% of our forceps deliveries were performed by specialists compared with only 16% of the vacuum extractions. We are aware of the limitations of this type of retrospective study. The most reliable method of comparing these methods of delivery would be a prospective study in which delivery was alternated between forceps and vacuum extraction. In clinical practice such a study is difficult.

In a recent study by Greis *et al.* (1981), a significantly higher maternal morbidity, such as lacerations and secondary anaemia, was found after forceps delivery than after vacuum extraction. The occurrence of third and fourth degree tears and cervical lacerations was 48% in the forceps group and 18% in the vacuum extraction group. In our study severe birth canal trauma occurred in 7% in both vacuum and forceps deliveries.

The study by Greis *et al.* (1981), like ours, was retrospective. According to these authors the distinct advantage of vacuum extraction is the markedly reduced need for anaesthesia. All our forceps deliveries were performed without general anaesthesia, which may have increased the gentleness of the operation; we used only local analgesia and in some patients epidural analgesia.

Low forceps deliveries have been usually considered safe for the infant (Pearse 1965; Ingardia & Cetrulo 1981). Friedman (1978), however, reported increased perinatal mortality after low forceps deliveries when protracted labour was the indication. Moolgaoker *et al.* (1979) compared different methods of instrumental delivery by the electronic measurement of compression and traction during delivery. With the exception of vacuum extraction, the overall duration of compression on the fetal head was less marked for instrumental than for normal delivery, due to the shorter delivery times. With vacuum extraction the overall traction forces were significantly greater than those associated with any of the forceps methods used. On the other hand Katz *et al.* (1982) concluded that the use of vacuum extraction during the second stage of labour lessened fetal depression, when compared with spontaneous delivery. Egge *et al.* (1981) reported that severe retinal haemorrhages were five times more common after vacuum extraction than after either forceps or spontaneous delivery. Retinal bleeding was also more extensive in the vacuum group. Recently Nilsen (1984) has reported that general intel-

Table 3. Infant birthweights and Apgar scores in forceps and vacuum extraction deliveries

	Forceps delivery (n=223)	Vacuum extraction (n=223)
Birthweight (g)		
<2500	6	2
2501–3000	15	13
3001–3500	68	57
3501–4000	84	99
≥4000	50	52
Apgar scores		
At 1 min		
0–3	4	10
4–6	13	26
7–10	206	187
At 5 min		
0–3	2	3
4–6	2	7
7–10	219	213

ligence at 18 years of age in their forceps group was significantly higher than the national average.

In a review article by Plauché (1979), a scalp abrasion or laceration occurred in 13%, cephalhaematomata in 6% and intracranial haemorrhage in 0·35% of the infants born by vacuum extraction. In our study the corresponding figures seem to be relatively high. All babies born by vacuum extraction have a 'chignon' of slightly raised, oedematous scalp beneath the cup site. Classic cephalhaematomata can accumulate beneath the periosteum of a single cranial bone because of the rupture of a diploic or emissary vein. These lesions often resolved slowly over a period of many weeks (Plauché 1979). Most of the lesions in our study disappeared in a few days and, evidently, were not classic cephalhaematomata. Intracranial bleeding presents a much more serious threat to the newborn than any scalp injury. One infant in our vacuum group had a cranial fracture, apparently due to the detachment of the cup on three occasions. In a report by O'Driscoll *et al.* (1981), among 36 420 consecutive first deliveries traumatic intracranial haemorrhage was seen at necropsy in 27 infants presenting by the head. All these were after forceps deliveries. More than half of these operations were classified as normal or easy. The frequency of forceps delivery in primigravidae fell from 30% in the early years to 10% in the late years of the study. Our operative delivery rate is low in comparison; forceps are used in 1% and vacuum extraction in 3% of deliveries and in recent years our caesarean section rate has been about 9%. Epidural analgesia has been used in 4–5% of our parturients.

We conclude that low forceps deliveries are safe for the infant and the mother and in our series fetal complications were less common after delivery by forceps than after vacuum extraction.

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The effect of interferon on human papillomaviruses associated with cervical intraepithelial neoplasia

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Summary. A double-blind, placebo-controlled, trial of leucocyte interferon showed that, contrary to previous reports, interferon had no significant effect on cervical intraepithelial neoplasia (CIN) when applied topically in a gel. DNA hybridization of cervical scrapes was used to monitor the effect of interferon on the human papillomaviruses (HPV) associated with CIN. There was, however, no significant difference in the expression of HPV 6 or 16 in the cervical epithelium of patients treated with interferon compared with those given a placebo. By using superficial cells scraped from the surface of the cervical epithelium as a source of DNA for viral studies, we were able to investigate the relation between HPV and CIN without interfering with the natural history of the disease. HPV 16 was detected in lesions which persisted while HPV 6 only was detected in one lesion that regressed. Regression was clearly associated with reduction in the number of copies of viral DNA per cell in this case. Dual infection with HPV types 6 and 16 were recorded in two patients with persistent lesions. In one patient, hybridization studies indicated that infection with HPV 16 could have occurred after infection with type 6 was established, and it is postulated that this may have changed the nature of the cervical lesion.

DNA analysis of cervical biopsy specimens has shown that human papillomavirus (HPV) DNA is present in 90% of specimens in which there are changes of cervical intraepithelial neoplasia (CIN) and in 70% of squamous cancers of the cervix (Gissmann 1984). The papillomaviruses have a well established potential for malignant transformation and an aetiological link between HPV infection, CIN and invasive cervical cancer has been proposed (Zur Hausen *et al.* 1984).

Interferon has both antineoplastic and antiviral properties and as such should be a particularly appropriate form of treatment for CIN and the HPV infection associated with it (Rager-Zisman & Bloom 1985). Indeed, Møller *et al.* (1983) reported partial or complete regression of CIN in six patients treated with interferon gel twice weekly for 12 weeks. However, the study was not controlled and the effect of the drug on

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the virus was not monitored. We report here a double-blind, placebo-controlled, trial of interferon for the treatment of CIN in which DNA hybridization techniques were used to monitor the effect of the drug on the papillomaviruses (Wickenden *et al.* 1985). This approach provided an insight into the role of HPV in the development and maintenance of the neoplastic lesions.

Patients and methods

Women with both cytological and colposcopical evidence of CIN 2 and/or 3 were selected for the study. The patients had one or more cervical smears showing moderate and/or severe dyskaryosis and an atypical transformation zone (ATZ) identified at colposcopy by the presence of acetowhite epithelium, mosaic and punctate patterns. The occurrence of the following sexually transmitted diseases or agents was sought: gonorrhoea, syphilis, candidosis, trichomoniasis, *Chlamydia trachomatis,* bacterial vaginosis, herpes simplex virus and genital warts. Where appropriate, treatment was given before entry into the study.

Patients over 35 years of age and those planning to become pregnant were excluded, as were those whose lesions extended beyond the visibility afforded by the colposcope, or with colposcopical evidence of invasion. Also excluded were patients with lesions that extended onto the vaginal fornices and, therefore, only women with small circumscribed lesions were accepted. Informed consent was obtained before therapy, the study having been approved by the ethics committee. The patients were assigned alternatively to one of two groups, one receiving treatment with interferon gel and the other receiving placebo.

Interferon

Human leucocyte interferon was produced according to the methods of Cantell *et al.* (1981) and partially purified by ethanolic precipitation to a specific activity of 10^6 international reference units/mg of protein. An interferon-containing gel was made by mixing the partially purified interferon with carboxymethylcellulose at 4°C. The resulting interferon gel (200 000 units/ml) was packed aseptically in 2 ml amounts in ampoules which were sealed and stored frozen (−20°C). Identical ampoules containing only carboxymethylcellulose gel were prepared also.

Interferon activity was determined as follows: 0·2 of the gel was thawed and diluted 1:10 (w/v) with medium containing 10% fetal calf serum. The mixture was homogenized in a vortex mixer for 2–3 min and then the interferon activity was determined by its ability to inhibit the cytopathic effect produced by vesicular stomatitis virus in an African green monkey kidney (VERO) cell line (Berg 1977). Inhibition of 50% of the cytopathic effect was taken as the end-point of the assay. Regular checks of the interferon activity were performed during the trial.

Previous studies have confirmed the stability of the interferon gel at −20°C. Interferon activity of the thawed gel reached a maximum after 5 h and remained for 48 h at 37°C (Møller *et al.* 1983).

Cervical cap

A 4 cm diameter plastic cap from Laboratorie CCD, Paris, was used (Fig. 1). All the gel from one ampoule was squeezed into the cap which was then applied to the cervix by the doctor and left in place for 24 h.

Management

At the first visit, a cervical scrape was taken with an Ayre's spatula and a smear prepared in the usual way. The tip of the spatula was broken off into 10 ml of phosphate-buffered saline (pH 7·2) for DNA studies (Wickenden *et al.* 1985). Then colposcopical examination was performed and acetowhite epithelium and mosaic and punctate patterns were noted and their location and extent recorded diagrammatically. The following demographic information was obtained: history of sexual activity, age at first intercourse, number of partners, contraceptive practice and smoking habits. The first cap containing either interferon or placebo was then applied to the cervix.

Applications of interferon (each of 400 000 units) or placebo were given twice weekly over a 6–8 week period (a total of 12 applications). The cap was removed by the patient after 24 h and during menstruation therapy was suspended.

Cytological and colposcopical examinations were repeated mid-way during treatment and on its completion. DNA studies were also repeated on completion. If any colposcopical or cytologi-

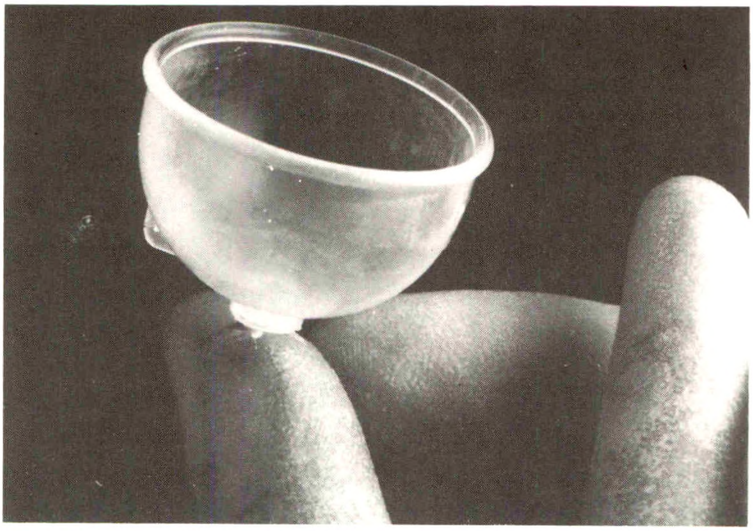

Fig. 1. Cervical cap (Laboratories CCD) used for application of interferon gel.

cal abnormality was detected at the end of the study, a colposcopically directed biopsy was assessed histologically before conventional laser therapy. If no abnormality was detected, patients were reviewed cytologically and colposcopically at 3-month intervals.

DNA studies

The cervical cells were pelleted and stored at −70°C until processed. DNA was extracted by proteinase K/SDS digestion followed by phenol extraction and ethanolic precipitation and spot-blotted onto a Zetapore nylon membrane (Bio-Rad Inc) using a 96-well suction manifold (Bio-Rad Inc). The filter was then placed in a solution of 0·5 mol/l sodium hydroxide, 1·5 mol/l sodium chloride for 1 min to denature the DNA, and then neutralized in a solution of 1·5 mol/l sodium chloride, 0·5 mol/l Tris HCl pH 8. Finally the filter was mixed in ×2 SSPE and baked for 3 h at 80°C. The filters were incubated at 65°C for 2 h in a solution of denatured salmon sperm DNA and prehybridized overnight in formamide solution to which denatured salmon sperm DNA had been added (Wickenden *et al.* 1985). They were then hybridized sequentially to radioactively-labelled probes for HPV 6, 16 and 18, and with a probe for an *Alu* repeat sequence. The latter occurs 5×10^5 times in the human genome and thus provides a sensitive assay for the total human DNA content of the sample. The probes were labelled with ^{32}P to a high specific activity using oligomeric primer extension (Feinberg & Vogelstein 1983). The filters were then left to autoradiograph onto preflashed Fuji-100 X-ray film for 2 weeks at −70°C. Following autoradiography, the probe was washed off the filters in the following solution: 0·5 × SSC, 1% SDS at 95°C cooling to 65°C, 3 × 1 h washes. The filters were then returned to the prehybridization stage described above for a subsequent hybridization. Autoradiographs were scanned on a Joyce Loebl Integrating Densitometric Scanner, and the area under each peak related to the quantity of DNA pipetted onto each individual spot. A calibration curve was then constructed and the mass of viral and human DNA in each sample was estimated. From these data, an estimate of the viral copy number per cell in each sample was obtained.

Results

Thirteen patients were assigned for treatment with interferon and a similar number were given the placebo. Demographic and sexual data and information on concurrent infections are presented in Table 1. Differences between the patients in the two groups were few and none had syphilis or herpesvirus infections.

As shown in Table 2, at the commencement of the study, 10 patients in the interferon group had cytological changes suggestive of CIN 3, two patients had changes suggestive of CIN 2/3 and one patient had changes suggestive of CIN 2. In the placebo group, seven patients had cytologi-

Table 1. Demographic, sexual and other features of patients

Feature considered	Interferon group ($n = 13$)	Placebo group ($n = 13$)
Age (years)		
Mean	25·7	25
Range	(18–34)	(20–34)
Married	1	3
Single	9	8
Separated	2	0
Co-habiting	1	2
Number of pregnancies		
0	8	6
1	2	3
2	1	2
⩾3	2	2
Smoker	9	9
Non-smoker	4	4
Contraceptive practice		
Oestrogen containing pill	9	6
None	2	4
Mechanical	1	2
Intrauterine device	1	1
Diseases		
Gonorrhoea	1	2
Candidosis	2	2
Trichomoniasis	1	2
Chlamydial infection	1	1
Vaginosis	4	5
Genital warts	3	1
Age at first intercourse (years)		
Mean	17	17·4
Range	(15–20)	(14–28)
Number of consorts		
Mean	9	11
Range	(1–30)	(1–30)
Number of years of sexual activity		
Mean	10	7·5
Range	(1–19)	(1–14)

cal evidence of CIN 3, one patient had evidence of CIN 2/3 and five patients had evidence of CIN 2. The cytological, colposcopical and histological changes at the end of the study are also presented in Table 2.

The final diagnosis assigned to each patient was based on the most severe abnormality detected on the completion of the study. The cervical lesions in five patients in the interferon group (patients 6, 8, 12, 20 and 26) and in nine patients in the placebo group (patients 3, 5, 7, 9, 13, 17, 19, 23 and 25) were unchanged by the respective treatments. There was, however, firm evidence that the lesions had regressed over the period of observation in two patients in the interferon group (patients 10 and 14) and in one patient in the placebo group (no. 1).

In the remaining patients, that is patients 2, 4, 16, 18, 22 and 24 in the interferon group and patients 11, 15 and 21 in the placebo group, the cytological, colposcopical and histological findings on completion of the study were at variance with each other and with the diagnosis on admission. However, it was considered that the lesions were unchanged in patients 2, 4, 11, 16, 18, 21 and 24 and that they had regressed in patients 15 and 22.

In summary, therefore, three patients (23%)

Table 2. The results of treatment on admission to and completion of the trial

Patient no.	Cytology on admission	Cytology on completion	Colposcopy on completion	Histological findings	Final diagnosis	HPV 6 DNA		HPV 16 DNA		*Alu*	
						on admission	on completion	on admission	on completion	on admission	on completion
Interferon group											
2	Severe dysk	Severe dysk	ATZ	Normal	CIN 3	ND	ND	ND	ND	ND	ND
4	Severe dysk	Severe dysk	ATZ	CIN 1	CIN 3	+++	–	+	+	+	+
6	Mod/severe dysk	Normal	ATZ	CIN 3/WVI	CIN 3	+	–	–	+	+	+
8	Severe dysk	Mod/severe dysk	ATZ	CIN 3/WVI	CIN 3	–	–	+++	+	+	+
10	Severe dysk	Normal	Normal	No biopsy	Normal	–	–	–	–	+	+
12	Severe dysk	Severe dysk	ATZ	CIN 2/3/WVI	CIN 2/3	–	–	+	+	+	+
14	Mod/severe dysk	Normal	Normal	No biopsy	Normal	US	US	US	US	US	US
16	Severe dysk	Severe dysk	ATZ	CIN 1/WVI	CIN 3	–	–	–	–	+	+
18	Mod dysk	Severe dysk	ATZ	WVI only	CIN 3	–	–	–	–	+	+
20	Severe dysk	Severe dysk	ATZ	CIN 3/WVI	CIN 3	–	–	+	–	+	+
22	Severe dysk	Normal	ATZ	CIN 1/WVI	CIN 1	–	–	–	–	+	+
24	Severe dysk	Mod dysk	ATZ	Normal	CIN 2	ND	ND	ND	ND	ND	ND
26	Severe dysk	Severe dysk	ATZ	CIN 3/WVI	CIN 3	ND	ND	ND	ND	ND	ND
Placebo group											
1	Mod dysk	Normal	Normal	No biopsy	Normal	++	–	–	–	+	+
3	Mod dysk	Mod/severe dysk	ATZ	CIN 3/WVI	CIN 3	ND	ND	ND	ND	ND	ND
5	Severe dysk	Severe dysk	ATZ	CIN 3	CIN 3	–	–	++	+	+	+
7	Mod/severe dysk	Mod/severe dysk	ATZ	CIN 2/WVI	CIN 2	–	–	++	+	+	+
9	Severe dysk	Mild dysk	ATZ	CIN 3/WVI	CIN 3	ND	ND	ND	ND	ND	ND
11	Severe dysk	Severe dysk	ATZ	Normal	CIN 3	–	–	+	+	+	+
13	Severe dysk	Severe dysk	ATZ	CIN 3/WVI	CIN 3	–	–	–	–	+	+
15	Severe dysk	Normal	ATZ	WVI only	WVI only	–	–	–	–	+	+
17	Severe dysk	Severe dysk	ATZ	CIN 3/WVI	CIN 3	–	–	+	–	+	+
19	Severe dysk	Severe dysk	ATZ	CIN 3	CIN 3	ND	ND	ND	ND	ND	ND
21	Mod dysk	Mod dysk	ATZ	Normal	CIN 2	–	–	+	–	+	+
23	Mod dysk	Mod dysk	ATZ	CIN 2	CIN 2	US	US	US	US	US	US
25	Mod dysk	Mod dysk	ATZ	CIN 2	CIN 2	ND	ND	ND	ND	ND	ND

All patients had an atypical transformation zone (ATZ) on admission.

WVI, Wart virus infection; Dysk, dyskaryosis; ND, not done; US, insufficient sample for assay.

+, 50–500 viral copies per cell; ++, >500–5000 viral copies per cell; +++, >5000 viral copies per cell.

Table 3. Association between human papillomavirus (HPV) 6 and 16 and cervical neoplasia

HPV 16 at start of trial	HPV 16 at end of trial	Number of patients	Lesion unchanged	Lesion regressed
+	+	6	6	0
+	−	3	3	0
−	+	1*	1	0
−	−	7	3	4†

+, Positive for HPV 16; −, negative for HPV 16.

* HPV 6 present at start of trial (patient 6); † present at start of trial in one patient (no. 1).

in the interferon group and two patients (15%) in the placebo group were considered to have responded to treatment ($P>0{\cdot}1$). Despite the fact that the majority of lesions failed to respond to treatment there was an overall clinical impression that in some cases the area of the ATZ was reduced. Application of the gel was not associated with any side-effects and the cervical cap was well tolerated.

DNA studies

Fifty-three samples were collected: hybridization with the *Alu* probe showed that all but two contained adequate DNA for viral studies. Viral sequences were detected in 28 of the 52 samples suitable for analysis. Lowest number of HPV 16 viral DNA copies per cell was 70 and the highest was 7000. For HPV 6 the respective figures were 15 and 1500.

A complete set of samples (at least one sample on admission to the study and one on completion) was obtained from 17 women; HPV DNA was detected in one or both samples from 11 of them (64%). Five of the women who were found to harbour HPV were being treated with interferon and six were receiving placebo. HPV 16 was detected in 10 patients (Tables 2 and 3). Of the nine patients who were positive for type 16 at the start of the trial, three had become negative at the end (Table 3). One patient who was negative for HPV 16 at the start of the trial became positive at the end (no. 6). However, in all cases the cervical lesion remained unchanged.

All samples were negative for HPV 18. However, evidence of infection with HPV 6 was observed in three patients (nos 1, 4 and 6). In all three viral DNA was present in the sample taken on admission and absent in the specimen taken on completion of the trial. In one patient (no. 1), there was a 100-fold reduction in viral DNA copy number concomittant with regression of the lesion. In patients 4 and 6 dual infection with type 16 was observed and the lesion persisted.

There were seven patients in whom viral DNA was not detected. Cervical neoplasia regressed in three and persisted in the others.

In summary, therefore, the prevalence of HPV DNA in the interferon-treated patients was not significantly different from that in the placebo group on admission or after treatment.

Discussion

Interferon has been used successfully for the treatment of genital warts (Schonfeld *et al.* 1984) and it has also been used to treat preneoplastic and neoplastic lesions at various body sites (Møller *et al.* 1983; Ikic *et al.* 1981). Moreover, the results of experimental studies using bovine papillomavirus transformed mouse cells have shown that interferon induces morphological reversion of the cells to their normal phenotype (Turek *et al.* 1982). We have shown that HPV DNA is present in the majority of cervices with CIN, and small, superficial, accessible lesions such as those seen in our patients should be amenable to topical treatment with this drug. However, we were unable to demonstrate that interferon treatment had a significant effect on regression of the CIN lesions or on expression of HPV DNA. This may have been due to inadequate penetration of the drug through the dysplastic epithelium and efficiency might be improved by using a vehicle that would increase transport of the interferon deeper into the tissues. In addition, the type of interferon may have been inappropriate for this type of lesion and gamma (immune) interferon may have been more effective. It differs from alpha interferon in that it is cytocidal rather than cytostatic and has a greater anticellular effect (Valle *et al.* 1975). Alpha-interferon has greater antiviral activity and therapy using a combination of both types of interferon may be worthwhile.

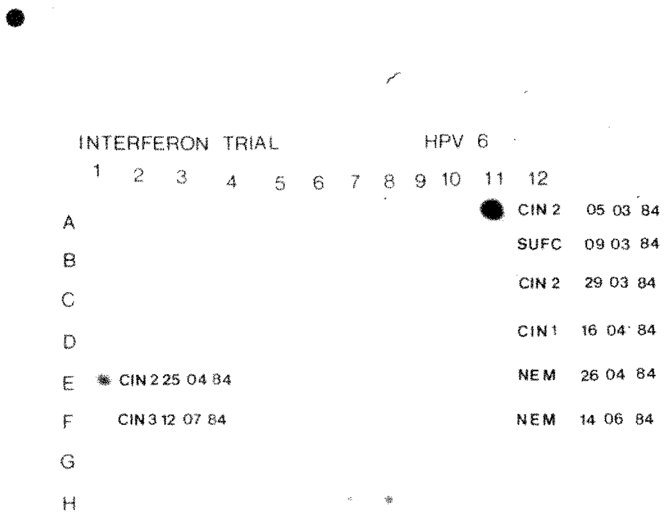

Fig. 2. Photograph of filter bearing DNA samples from interferon trial patients, hybridized to a probe for HPV 6. The dates the samples were taken and the corresponding cytological findings for each specimen were recorded to the right of the DNA spots (SUFC = unsatisfactory smear, NEM = no evidence of malignancy). Six DNA samples from case 1 are shown in columns 11 A–F. Two DNA samples from case 6 are shown in column 1E and 1F. The diminishing signal strength concomitant with regression of the lesion in case 1 can clearly be seen in the photograph (column 11). Note also the disappearance of HPV 6 signal in the samples from case 6) column 1, samples E1 and F1). This patient subsequently progressed to CIN 3, with the appearance of a strong HPV 16 signal (see Fig. 3).

Our findings contrast with those of Møller *et al.* (1983) who reported partial or complete regression of lesions in six patients treated with interferon gel twice weekly for 12 weeks. However, the study was uncontrolled and the cases were not classified as CIN 3, but rather as dysplasia and this can regress spontaneously. Also, cervical biopsy specimens were taken at intervals before and during the study, a procedure which is known to affect the natural course of CIN (Jordan *et al.* 1964). In contrast, we selected patients in which the lesions were unlikely to regress over a 6–8 week period and used non-invasive techniques to monitor the lesions, deferring biopsy until the trial was complete.

Because laser therapy is so effective in the majority of patients with CIN, especially for the circumscribed lesions selected for this study, a more aggressive approach using systemic interferon could not be justified. However, there are a group of patients with intraepithelial neoplasia for whom laser therapy is inappropriate and in whom treatment with systemic interferon could be justified despite the side-effects (Scott *et al.* 1981). These are patients with multicentric genital-tract neoplasia involving the vagina or vulva, or patients with residual and recurrent vault lesions after hysterectomy for CIN. These patients present a serious clinical problem and may be prepared to tolerate the discomfort of systemic interferon therapy rather than radical vulvectomy or vaginectomy.

This is the first study in which DNA hybridization techniques have been used to monitor the effect of interferon on HPV infection in the female genital tract. Previous therapeutic trials of interferon on genital warts have relied on morphological studies to determine the effectiveness of therapy. The results of several studies have shown that subclinical infections with HPV do not always induce the morphological changes that are characteristic of these viruses and reliance on morphology alone may lead to errors in the diagnosis of this infection (McCance *et al.*

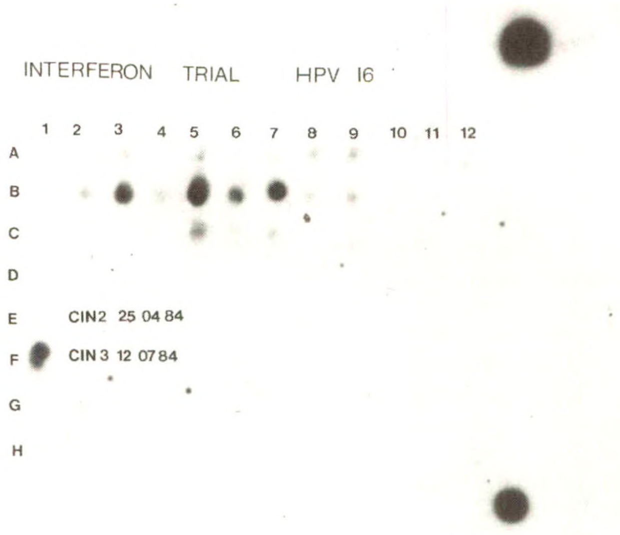

Fig. 3. Photograph of same filter bearing DNA samples from interferon trial patients hybridized to a probe for HPV 16. The appearance of a strong HPV 16 signal in case 6 (samples E1 to F1) can be seen in the sample F1. This was associated with progression of the CIN lesion from CIN 2 to CIN 3 over a period of 3 months. There was no hybridization of HPV 16 to any of the samples from case 1 (column 11A to 11F).

1983; Walker *et al.* 1983; Wickenden *et al.* 1985). DNA hybridization is more sensitive than cytology, colposcopy or histology as a method of detecting HPV infection and, unlike these methods, permits identification of specific virus types and an estimate of the copy number per cell of viral DNA in the sample, a further reason for its use in this study.

We have used cells scraped from the superficial layers of the cervical epithelium with an Ayre spatula as the source of DNA for viral studies. This non-invasive approach has several advantages over the more conventional method of studying the prevalence of HPV DNA in the cervix that uses surgical biopsy material as a source of DNA. It has enabled us to compare the cytological and virological findings in the same sample and thereby study the relation between HPV infection and CIN 3 prospectively without interfering with the course of the disease. There was a close correlation between the presence of dyskaryotic cells in the Papanicolaou smear and the presence of HPV DNA in the corresponding sample. Dyskaryotic cells suggestive of CIN were detected in smears corresponding to 24 of the 28 samples containing viral sequences. In the four remaining samples the smear was reported as negative or unsuitable for cytology due to a heavy inflammatory exudate, thus confirming previous reports that the presence of HPV in the cervix is not always reflected in the cervical smear (Wickenden *et al.* 1985).

Viral sequences were not detected in 16 samples although the corresponding cervical smear contained dyskaryotic cells. This could be attributed to low levels of HPV DNA in the sample and reflect the limits of sensitivity of the hybridization technique which, under the stringent conditions applied in this study, cannot detect less than 5 pg of HPV DNA in the sample. This is equivalent to 10^5 virus sequences or approximately one virus DNA copy per cell. Although there appears to be some cross hybridization in heavily overloaded calibration samples of pure viral DNA, we have established the specificity of this technique on the relatively lower levels of viral DNA present in clinical samples (C. Wickenden *et al.* unpublished observations). Certainly, the sensitivity of the hybridization procedures is low and needs to be improved if this technique is to be more widely used for diagnostic research. This may be achieved without loss of specificity by using single stranded probes cloned in the M13 vector. It should, however, be borne in mind that the negative DNA findings in these samples may be due to papillomaviruses other than HPV 6, 16 or 18 in the cervix (Gissmann 1984).

It has been suggested that CIN lesions associated with HPV 16 or 18 are more likely to progress to invasive cancer than those associated with types 6 or 11 and long-term prospective studies of CIN are needed to verify this hypothesis (Gissmann 1984). The non-invasive techniques developed for this study are particularly appropriate for this task. Our study, although of relatively short duration, has already proved very informative. We have confirmed earlier reports that HPV 16 is the most common wart virus type to be found in CIN and demonstrated type 16 DNA only in those lesions that tended to persist. We also have clear evidence of regression of CIN associated with local infection with HPV 6 (patient 1). HPV 6 DNA copy numbers per cell fell markedly as the cervix returned to normal in this patient. The patient has been followed for 18 months and no recurrence noted (Fig. 2). In addition, dual infection with type 6 and 16 was recorded in two patients (nos 4 and 6). In one of them (patient 6) the data suggest that infection with type 16 could have occurred after infection with type 6 (Figs 2 and 3) and may have changed the nature of the lesion. Further studies are in progress to investigate this hypothesis.

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Alpha interferon in human pregnancy

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Summary. The concentration of interferon-alpha was measured by a specific two-site immunoradiometric assay in a variety of fluids and tissues collected during human pregnancy. Maternal blood and blood and tissues from non-pregnant adults contained little or no interferon-alpha. Fetal blood, fetal organs, placenta, membranes, amniotic fluid and decidua all contained significant and roughly equivalent amounts ranging from 1·1 to 10 u/ml (or per g of tissue). These findings demonstrate that the fetus and its immediate surroundings are permeated with interferon. It is suggested that this may play a role in regulation of the maternal-fetal graft relation.

The interferons are a group of powerful inducible effector molecules that can be produced by virtually all animal cells. They are able to modify basic biochemical processes in a highly selective and reversible fashion, the most familiar effect being their role in the natural process of recovery from viral infections (Burke 1985). Additionally, they cause general inhibition of cell growth, have complex immunomodulatory effects, reverse neoplastic phenotypes, and stimulate or prevent cell differentiation. Usually, but not invariably, interferons exert their effects only on cells of homologous species. Based on immunochemical studies, human interferons have been divided into three major antigenic types: alpha (leukocyte); beta (fibroblast); and gamma (immune). The genes for alpha and beta have been clearly characterized and in the case of interferon-alpha include a multiplicity of subtypes coded by at least 10 genes (Goeddel *et al.* 1981).

Information on interferons in relation to pregnancy and the fetoplacental unit is limited (Table 1). In common with the adult, most fetal tissues appear to be able to synthesize interferon in response to viral induction. In man, the amnion can synthesize interferon in the absence of inducers, and it can be found in both normal amniotic fluid and fetal blood, but none of the existing studies can specify or exclude sources for the interferon.

The recent development of specific and sensitive immunoradiometric assays for human interferon-alpha (Abbott *et al.* 1984; Scott *et al.* 1985; Koscielniak *et al.* 1985) presents an opportunity to examine in more detail the presence and distribution of interferon in the human fetoplacental unit.

Materials and methods

Various fluids and tissues were collected from unselected pregnancies presenting for termination in the first (16 women at 8–12 weeks) and second trimesters (21 women at 14–24 weeks), and at the time of caesarean section or vaginal delivery in the third trimester (11 women). The specimens included: maternal blood (16 specimens); umbilical cord blood (15 specimens); amniotic fluid (153 specimens); placenta (23 specimens); fetal membranes (39 specimens); maternal decidua (9 specimens); and fetal organs (41 specimens, including lung, heart, thymus, thyroid, adrenal, intestine, skeletal muscle, skin and brain at 10–22 weeks gestation). In addition, 14 blood samples and nine extracts from tissues including pyloric antrum,

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Table 1. Studies on interferon (IFN) in relation to pregnancy

Reference	Findings
Banatvala *et al.* 1970	Normal IFN response of human fetal cells to virus induction
Overall & Glasgow (1970)	Virus infection of ewe produced low IFN response in mother but very high levels in fetus
Ray (1970)	Normal IFN response of human fetal cells to virus induction
Fowler *et al.* (1980)	IFN present at high concentration in mouse placenta, but not in maternal or other fetal tissue
Lebon *et al.* (1982)	IFN-alpha present in normal human amniotic fluid
Sorrentino *et al.* (1982), Lorenzetti *et al* (1984)	Cultured human amniotic cells can release IFN-beta after viral induction
Duc-Goiran *et al.* (1983)	Cultured human amniotic cells can release IFN after viral induction
Barlow *et al.* (1984)	Mouse embryo tissues produce IFN in response to viral induction from 7th day of development
Duc-Goiran *et al.* (1985)	IFN present in samples of fetal blood, placenta and membranes
Evans *et al.* (1985)	IFN administered to mouse not transferred from mother to fetus IFN inducible in both mother and fetus.
Bocci *et al.* (1985)	IFN produced by perfused human term placenta
Nakane *et al.* (1985)	Maternal IFN response to *Listeria* infection in mice suppressed during pregnancy.
Yamada *et al.* (1985)	IFN present in mouse placenta

All of these studies were based primarily on biological assays.

duodenum, colon, and pancreas from non-pregnant adults were examined. All tissue specimens were processed as rapidly as possible. After washing to remove blood the material was divided with scissors, washed again, and excess fluid removed before weighing. The tissue was suspended in 0·1 mol/l phosphate buffered saline (pH 7·4) containing 0·1% bovine serum albumin (approximately 1 ml buffer per g tissue). The suspension was extracted for 60 s in an Ultra Turrax homogenizer. All fluids and tissue extracts were immediately centrifuged at 3500 *g* for 30 min and stored in aliquots at −20°C.

Human interferon-alpha was measured using a two-site immunoradiometric assay (Boots-Celltech Diagnostics Ltd). This assay used a rat monoclonal antibody (designated YOK 5/9) which was originally produced by Dr S. Secher, MRC Laboratory of Biology, Cambridge. The minimum detection limit of this assay is quoted as 0·5 u/l, but to exclude the occasional marginally positive result at or very close to this limit, we adopted 1·0 u/l as the cut-off point. The within- and between-assay coefficients of variation for this procedure were assessed at 4·2% ($n = 10$) and 6·0% ($n = 3$) respectively. All results were expressed per ml of fluid or per g wet weight of tissue.

Results

Interferon-alpha was not detected in maternal blood during pregnancy. Low levels were apparent in two out of 15 non-pregnant women. Positive levels were found in 60% of fetal blood samples, and similar levels were found in fetal organs (Table 2, Fig. 1). Significant levels of interferon-alpha were also found in amniotic fluid, placental tissue, fetal membranes, and maternal decidua (Table 2, Fig. 1). Insofar as could be judged from the materials available, there was no change in interferon-alpha levels in any of these sites during the course of the pregnancy (Fig. 2). Although the levels appeared to be slightly higher in decidual than in other sites (Table 2), the numbers were small and the difference was not statistically significant (Mann–Whitney test).

Discussion

This investigation confirms earlier findings on the presence of interferon-alpha in the human fetoplacental unit (Table 1). Furthermore, it extends these observations by demonstrating that relatively high levels can be detected in all fetal tissues, including blood, and in all those tissues which constitute the interface between

Table 2. The concentration of interferon (IFN)-alpha in various tissues and fluids during human pregnancy.

Tissue/fluid	No. of specimens	Positive results (%)	IFN-alpha concentration (u)	
			Median	Range
Normal blood	16	13·0	—	—
Normal tissues	9	11·0	—	—
Maternal blood	16	0	—	—
Fetal blood	15	90·0	1·6	1·2–4·4
Amniotic fluid	153	74·0	2·8	1·1–9·9
(≤24 weeks)	95	80·0	1·85	1·1–9 9
(>24 weeks)	58	65·0	2·3	1·3–7·8
Placenta	23	96·0	2·6	1·1–10·0
Membranes (incl cord)	39	85·0	2·8	1·1–10·0
Decidua	9	80·0	5·5	1·9–10·0
Fetal organs	41	72·5	2·8	1·1–14·9

The results are expressed as units per ml of fluid or per gram wet weight of tissue.

maternal and fetal tissues (i.e. placenta, fetal membranes, and maternal decidua). In common with other membrane/decidual products, interferon-alpha also appears in amniotic fluid. Thus, the human fetoplacental unit appears to be entirely permeated and surrounded by interferon, very little of which reaches the mother.

On the basis of the present findings we are unable to specify the exact anatomical site of origin of the interferon-alpha in the human fetoplacental unit. Unlike Duc-Goiran *et al.* (1985) we did not find especially high levels in the placenta itself. It is likely that the source of the interferon is white blood cells. Leucocytes of both maternal and fetal origin are found in the sites in which interferon-alpha is present, though given the multiplicity of fetal tissues involved it would seem that fetal white cells must predominate. But normal cells, including leucocytes, do not produce interferon in the absence of an inducer; indeed, production is stringently repressed. Many agents can induce interferon including all major classes of viruses, bacterial endotoxins, double-stranded RNA (dsRNA),

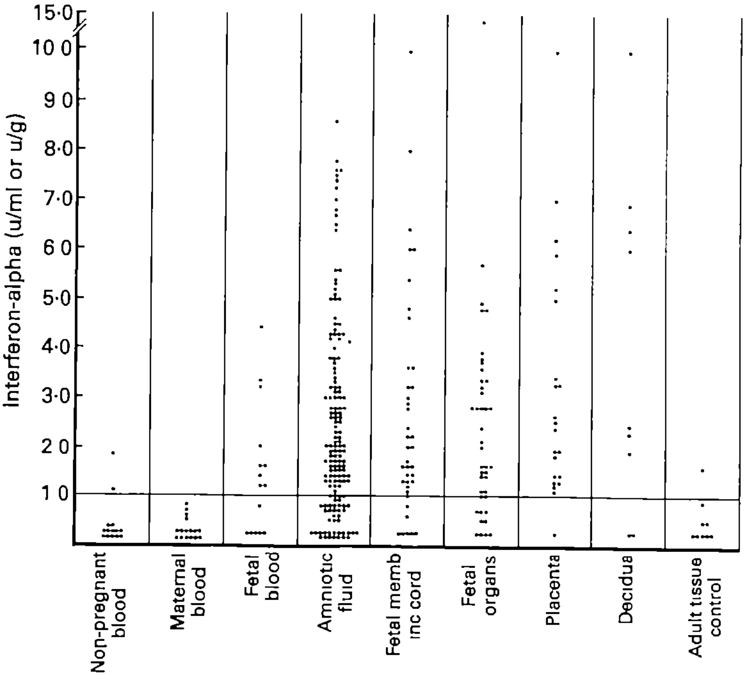

Fig. 1. Levels of interferon-alpha (IFNα) in various sites in human pregnancy.

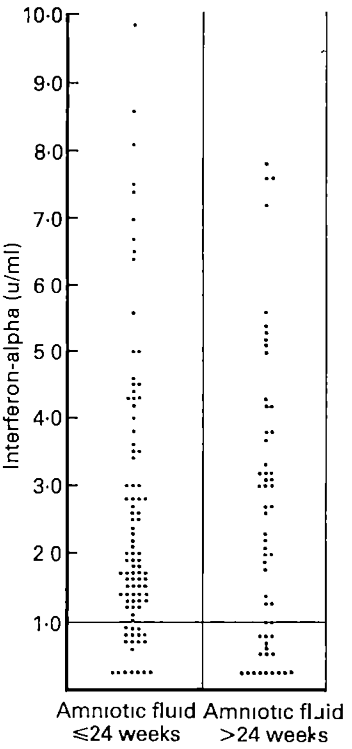

Fig. 2. Levels of interferon-alpha (IFNα) in amniotic fluid in the first and second halves of pregnancy.

foreign proteins and mitogens. There is no evidence for the action of any of these specific factors in relation to human pregnancy—especially since interferon production seems to be a common phenomenon. However, it is well-recognized that the contact between fetal and maternal tissues yields the potential for a classic homograft reaction (maternal v fetal or *vice versa*) In consequence the area of contact (chorion-decidua) has been addressed in the search for factors which are responsible for the preservation of the fetus as a homograft. In view of the known immunomodulatory properties of interferon (Bergeret *et al.* 1980) and the fact that interferon can inhibit cell growth (Dahl & Degre 1976; Evinger *et al.* 1981), it is at least possible that interferon might be such a factor in human pregnancy. Alternatively, these molecules may be produced as part of the general process of replication and differentiation of fetal tissue.

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Enhanced phagocytosis of mononuclear phagocytes in pregnancy

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Summary. The phagocytic activity of peripheral blood mononuclear phagocytes for *Staphylococcus epidermidis* of healthy non-pregnant and pregnant women throughout pregnancy was examined in relation to gestational age. The study included 30 healthy non-pregnant women and 90 healthy pregnant women equally distributed across the three trimesters. Two variables were investigated: the number of mononuclear cells in phagocytosis and the average number of bacteria per monocyte in phagocytosis. As pregnancy progressed a gradual and significant increase was found in the number of monocytes in phagocytosis and a significantly higher proportion of macrophages with six or more bacteria per phagocyte.

Mononuclear phagocytes play a major role in immunity, both innate and acquired, due to their ability to phagocytose and destroy bacteria, secrete a great number of substances and collaborate with the lymphocytes in the immune response (Walker & Hester 1984). In pregnancy where defective T-lymphocyte function has been reported by some (Stites & Siiteri 1983; Weinberg 1984), but not all authors (Baboonian & Griffiths 1983), the role of mononuclear phagocytes may be more important to secure protection for both mother and fetus, particularly because the fetal immune system is not yet fully developed.

Experiments in pregnant rats and mice (Nicol *et al.* 1965; Graham & Saba 1973; Sljivic *et al.* 1975) indicate an enhanced activity of the mononuclear phagocytes. In man, the influence of pregnancy on the mononuclear phagocytes has not been investigated to a similar extent although there is evidence of a similar activation (Plum *et al.* 1978; Hawes *et al.* 1980; Meltzel & Silva 1980; Salvaraj *et al.* 1982).

In this study we have examined the phagocytic activity of peripheral blood mononuclear phagocytes from healthy non-pregnant and pregnant women.

Subjects and methods

The study included 120 healthy women between 20 and 40 years of age, 30 of them were not pregnant and the other 90 were healthy pregnant women comprising 30 in each of the three trimesters of pregnancy.

All the women were residents of the Greater Athens area and were either seen at the University Maternity Clinic of Alexandra Hospital or admitted to the same hospital for delivery. A 15-ml sample of heparinized venous blood was taken from each woman and transferred within 30 min to the laboratory for processing under

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code. Each experiment included one woman from each of the four groups and care was taken that the women tested in the same experiment were of the same age (±3 years).

Mononuclear cell separation

Monocytes were isolated from the peripheral blood by a modification of the technique described by Koller *et al.* (1973). A 15-ml volume of heparinized venous blood was mixed with an equal volume of MEM F14 medium (GIBCO BIO-CULT) and divided into two equal portions in two plastic centrifuge tubes of 25 ml (Sterilin). The mixture was layered over 15 ml of Lymphoprep (Nyegaard & Co., Oslo, Norway) and centrifuged at 400 *g* for 30 min. The interface, containing mononuclear cells and platelets, was harvested with a Pasteur pipette and the two portions were combined and transferred to a 25 ml plastic centrifuge tube. The suspension of cells was diluted with 15 ml of medium, and 3 ml Lymphoprep was added beneath the cell suspension. The preparation was then centrifuged at 200 *g* for 10 min. With this procedure the mononuclear cells were separated at the bottom of the centrifuge tube while most platelets remained in suspension. The supernatant was removed and the cells were resuspended in 15 ml MEM F14. A fresh 3 ml of Lymphoprep was added beneath the cell suspension and the low speed centrifugation was repeated. The supernatant was discarded, the mononuclear cells were suspended with 15 ml MEM F14 medium and were centrifuged at 300*g* for 15 min. The pellet of mononuclear cells was suspended in MEM F11 medium, containing calcium to which 200 U/ml penicillin was added so that the final suspension contained 2 × 10^6 cells/ml. Aliquots of 100 μl were transferred on clean 18 × 18 mm coverslips placed in plastic petri dishes and incubated for 30 min at 37°C in 5% CO_2. The coverslips were washed three times with Hanks BSS (GIBCO BIO-CULT) and the phagocytic activity of the adherent cells was tested. These cells, on a morphological basis, consisted mostly (95%) of mononuclear cells.

All experimental steps were performed at room temperature. Due to the short duration of experiment it was not considered necessary to include serum in the culture medium in order to avoid its possible effect on the cells studied.

Preparation of Staphylococcus epidermidis

A strain of *S. epidermidis* obtained from the Department of Microbiology of the Medical School of the University of Athens maintained on Brucella agar (DIFCO) was used. Bacteria were grown overnight in nutrient broth (DIFCO), washed with 0·9% NaCl and inactivated at 60°C for 30 min. They were resuspended in 0·9% NaCl, washed twice in 0·9% NaCl and were then resuspended in MEM F_{11} in a concentration of 5 × 10^6 bacteria/ml.

Test for phagocytosis

A 0·5-ml sample of the bacterial suspension was placed on the coverslips with the adherent mononuclear cells and incubated in 95% air/5% CO_2 for 30 min at 37°C. The coverclips were washed six times with Hank's BSS to remove the non-phagocytosed bacteria. Following the washing procedure two of the coverslips were dried at room temperature, stained with May–Grunwald Giemsa and examined by light microscope under × 1000 magnification. The two remaining wet coverslips were stained with Evans blue and were examined by phase contrast microscopy. Evans blue does not enter the intact cell and thus stains only bacteria which are not phagocytosed. A total of 400 cells was counted on each slide. The number of mononuclear cells in phagocytosis and the average number of bacteria per monocyte in phagocytosis were recorded.

Results

To simplify the presentation of the results the 30 women of each group were divided in six subgroups according to the number of macrophages in phagocytosis (0–9, 10–19, 20–29, 30–39, 40–49, >50) and in three subgroups according to the average number of bacteria per phagocyte in phagocytosis (1–3, 4–5, >6).

Number of macrophages in phagocytosis

Table 1 shows the frequency distribution of non-pregnant women and of pregnant women in the first, second and third trimester of pregnancy by number of macrophages in phagocytosis. A gradual increase in the number of monocytes in phagocytosis with the duration of pregnancy is evident. The χ^2 test (Armitage 1955) was applied to test the trend in the proportion of macro-

Table 1. Frequency distribution of non-pregnant and pregnant women in the 1st, 2nd and 3rd trimester of pregnancy by number of macrophages in phagocytosis (400 macrophages examined for each woman)

	Number of macrophages in phagocytosis						
Groups of women	0–9	10–19	20–29	30–39	40–49	≥50	Total
Non-pregnant	1	21	8	0	0	0	30
1st trimester	1	2	27	0	0	0	30
2nd trimester	0	0	4	16	9	1	30
3rd trimester	0	0	0	1	10	19	30

χ^2 for trend non-pregnant/1st trimester = 18·8 $P<10^{-5}$

χ^2 for trend 1st trimester/2nd trimester = 34 $P<10^{-8}$

χ^2 for trend 2nd trimester/3rd trimester = 31·4 $P<10^{-7}$

phages in phagocytosis. The proportion of macrophages in phagocytosis was significantly lower among non pregnant than among women of the first trimester, among women of the first trimester than among women of the second trimester, and among women of the second trimester than among women of the third trimester.

Number of bacteria per macrophage in phagocytosis

Table 2 shows the frequency distribution of macrophages in phagocytosis by number of *S. epidermidis* per macrophage and by stage of pregnancy. It appears that among pregnant women there is not only a higher number of macrophages in phagocytosis but also a higher proportion of these macrophages with six or more bacteria per phagocyte (39% vs 28% $\chi^2=23{\cdot}5$ $P<10^{-5}$). Furthermore, women in the first trimester have a lower proportion of multi-phagocytosing macrophages than women of the other two trimesters (34% vs 41% $\chi^2=8{\cdot}8$ $P=0{\cdot}003$).

Controlling for the number of macrophages in phagocytosis by stratification and application of the Mantel extension procedure (Mantel 1963) did not affect, to any substantial degree, the above results. On the other hand the number of bacteria per macrophage in phagocytosis did not increase in a regular way with duration of pregnancy, although overall the proportion of macrophages in phagocytosis with more than six bacteria per macrophage was higher among pregnant than among non pregnant women. Taking these results together they indicate that pregnancy increases the proportion of macrophages capable of phagocytosis, as well as the quantitative dimension of the phagocytic potential of the individual macrophage. Both phenomena appear to be related to the duration of pregnancy but the association is stronger with respect to the first.

Discussion

To evaluate the phagocytic activity of peripheral blood mononuclear phagocytes two variables were studied: the number of cells in phagocytosis and the average number of bacteria per cell in phagocytosis. It was found that the phagocytic activity of blood mononuclear pha-

Table 2. Frequency distribution of macrophages in phagocytosis by number of bacteria *(Staphylococcus epidermidis)* per macrophage and by stage of pregnancy

	Non-pregnant women		Stage of pregnancy (trimester)						
			First		Second		Third		
Number of bacteria per phagocyte		(%)	*n*	(%)	*n*	(%)	*n*	(%)	Total
1–3	228	(45)	266	(42)	414	(38)	574	(38)	1482
4–5	134	(27)	155	(24)	223	(20)	330	(22)	842
6+	141	(28)	219	(34)	460	(42)	598	(40)	1418
Total	503	(100)	640	(100)	1097	(100)	1502	(100)	3742

gocytes for *S. epidermidis* was significantly increased in pregnant women and an increase with duration of pregnancy was observed for the number of cells of phagocytosis.

The increased phagocytic activity of peripheral blood monocytes in pregnant women observed in this investigation and the increase of in-vitro random migration of monocytes from pregnant women during their second and third trimesters (Hawes *et al.* 1980) imply that in pregnancy there is a significant activation of mononuclear phagocytes. The results of these two studies and the reported increase in the number and proportion of monocytes in the peripheral blood (Plum *et al.* 1978; Hawes *et al.* 1980) suggest that in pregnancy there is a strong stimulation of the mononuclear phagocytic system. This activation may balance the increased needs for protection of both the mother and the fetus. The mechanisms which lead to this activation are not understood although immunological and hormonal factors have been postulated. Animal models suggest that pregnancy provides an immunological stimulus since histological changes of lymphnodes draining the pregnant uterus are similar to those seen during antigenic stimulation (Beer & Billingham 1974; Ansell *et al.* 1978). In man, the variety of anti-HLA antibodies found in multiparous women (Van Rood & Eerniss 1958; Payne & Rolfs 1958; Talwar 1980) imply that during pregnancy women are under continuous antigenic stimulation. On the other hand, oestrogen treatment increases clearance rate of intravenously injected particles in animals (Nicol *et al.* 1965; Cordingley 1969) and man (Margarey & Baum 1971). The trend of increased phagocytic activity of peripheral blood monocytes, observed in this study, is compatible with the suggestion that continues stimulation by high levels of oestrogens and by fetal tissue antigens may be responsible for the activation of the mononuclear phagocytic system.

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Ovulation after treatment with ethinyl-oestradiol and medroxyprogesterone acetate in a woman approaching premature menopause. Case report

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Case report

The 32-year-old patient was referred to the gynaecological-endocrine clinic in February 1984 with a 6-year history of primary infertility. Menarche had been at 12 years and her periods were regular every 28–30 days until 1 year previously, when they became more erratic (every 20–40 days). Laparoscopy in October 1981 had revealed normal ovaries and pelvic anatomy with patent tubes on dye test. Her husband's semen analysis and a mid-cycle post-coital test were also normal. In May 1982 she had a laparotomy for a right ovarian cyst, 3·5 cm in diameter, which was removed. On histology it was found to be a dermoid cyst. The remainder of the right ovary was not removed.

On examination in 1984 she was healthy, weight 56 kg, height 154 cm, with normal secondary characteristics and no acne, hirsutism or galactorrhoea. Her uterus and ovaries were normal on palpation.

A baseline ultrasound scan showed that both ovaries were normal in size and texture. Her husband's semen analysis was normal. Hormone determinations on the last day of a menstrual cycle were: luteinizing hormone (LH), 9·3 u/l; follicle stimulating hormone (FSH), 8·1 u/l; oestradiol (E_2), 544 pmol/l, progesterone 7·3 nmol/l; prolactin, 152 mu/l; these were all within the normal follicular phase range apart from E_2 which was in the range for the mid-luteal phase of a normal cycle.

Endocrinological studies

Hormonal studies of three spontaneous cycles

Blood samples were obtained 2–3 times weekly for determination of LH, FSH, E_2 and progesterone as described previously (Petsos *et al.* 1985). In the second of these studies in addition serial ovarian ultrasound scans were performed to monitor follicular development and ovulation (Petsos *et al.* 1985).

The first cycle studied (March 1984) was 30 days in length. LH levels were borderline high and FSH levels persistently high throughout the luteal phase. E_2 levels rose modestly during the mid-cycle and remained low during the luteal phase, whereas progesterone attained high normal levels (Fig. 1).

The second cycle studied (April–May 1984) was 20 days in length, with an apparently short follicular phase. A modest LH peak was recorded on Day 5 of the cycle. During the luteal phase levels of both gonadotrophins were borderline low, whereas a dissociation of E_2 and progesterone secretion was again seen: E_2 levels were low and progesterone levels normal. Ultrasound scans from Day 7 of the cycle 2 days after the LH surge showed development of a small cystic structure during the middle of the luteal phase (Fig. 2).

The hormonal profile was assessed without ultrasound over a 30-day period (September–October 1984), which in the event included the luteal phase of one cycle and the whole of the following cycle (Fig. 3). The hormone findings were bizarre and abnormal throughout. During the first of the luteal phases LH and FSH levels were high and E_2 levels exceptionally so (up to 2230 pmol/l); progesterone on this occasion was

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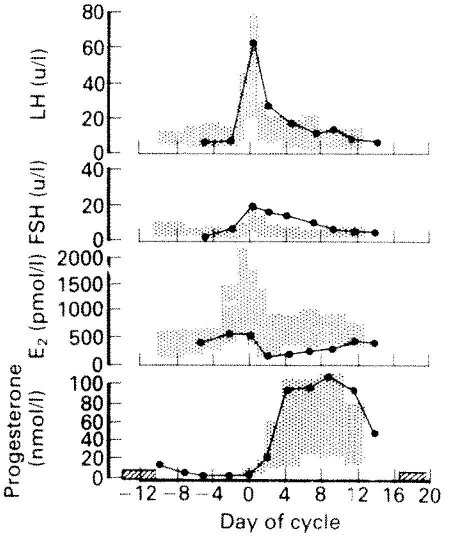

Fig. 1. Endocrine pattern in the first spontaneous cycle studied. Stippled area in this and subsequent figures indicates 95% confidence limit in 30 ovulatory cycles lined up by the day of LH peak (Petsos *et al.* 1985); hatched bars indicate menstruation.

within the normal range for the luteal phase. Menstruation ensued when progesterone declined in the presence of persistently high levels of circulating E_2 (670 pmol/l). The following cycle was characterized by a very short follicular phase, with a LH peak recorded on Day 7. LH levels were normal throughout and FSH levels high during the luteal phase.

In summary, all three spontaneous studied cycles were abnormal. The most consistent abnormalities observed were inappropriate elevation of FSH and short follicular phase (each observed in two cycles). These findings are compatible with those recorded previously in women in the menopausal transition (Sherman & Korenman 1975) and on that basis a diagnosis was made of impending premature menopause.

Suppression studies

Ethinyl-oestradiol (EE_2), 30 µg daily, was given for 6 weeks and medroxyprogesterone acetate (MPA), 5 mg daily, for the first 4 weeks and 5 mg twice daily for the remaining two. Treatment was then stopped for a week to allow a withdrawal bleed. The patient was then put on the same treatment (EE_2, 30 µg daily, and MPA, 5 mg twice daily) for a further 4 weeks.

The weekly hormone results while on treatment are shown in Fig. 4. Suppression of LH and FSH to approximately 5 u/l was achieved within a week. After the week off suppression gonadotrophin levels had apparently rebounded but were subsequently suppressed during the second course of treatment. E_2 levels remained high (>660 pmol/l) over the first 4 weeks of treatment and then dropped to undetectable levels; then during the second course of treatment E_2 levels rose again, to decline again to low levels before the end of treatment. Progesterone levels were undetectable throughout.

Post-treatment studies

The two consecutive cycles following the suppression, shown in Fig. 5, were monitored by serial hormone determinations and ultrasound scans. LH, E_2 and progesterone levels were normal but FSH levels rose abruptly to remain high throughout the first cycle. As expected FSH tended to suppress when E_2 levels rose in the preovulatory and mid-luteal phases. Ultrasound monitoring revealed a follicle in the left ovary which reached a diameter of 22 mm by the day of the LH peak and within the following 48 h collapsed, consistent with ovulation.

Unfortunately, during the second cycle after suppression a batch of four specimens collected in the follicular phase were lost. Nevertheless, the available results give the overall hormone

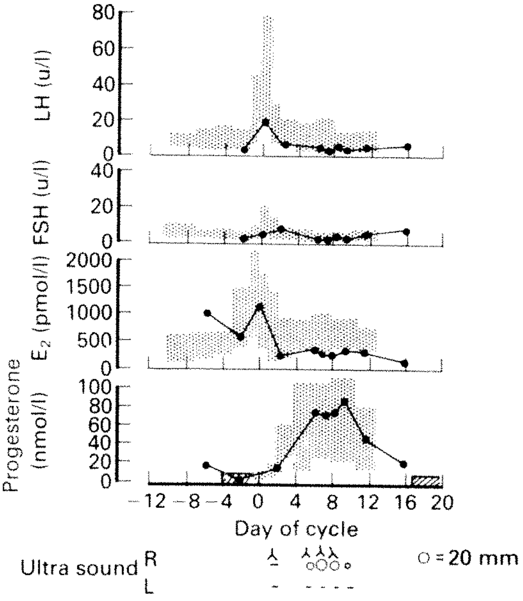

Fig. 2. Endocrine patterns in the second spontaneous cycle with an apparently short follicular phase.

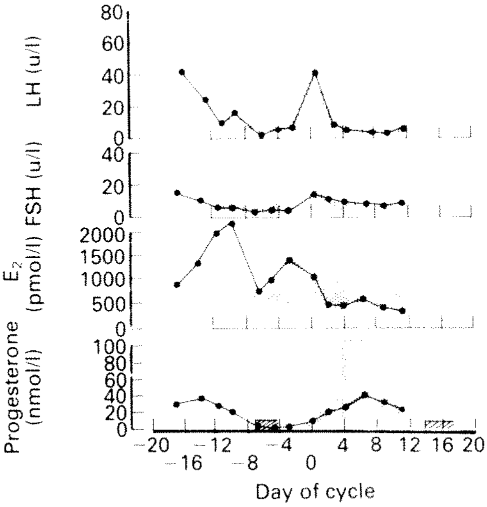

Fig. 3. Hormonal observations over a 30-day period in which were included the luteal phase of a spontaneous cycle and the whole of the following spontaneous cycle.

profile. LH and FSH levels were high in both phases of the cycle. Menstruation ensued in the presence of high E_2 levels (690 pmol/l). During the luteal phase E_2 levels were normal and progesterone levels borderline low. Ultrasound scans started on the first day of the cycle when a follicular structure of 21 mm in diameter was seen. This reached a maximum diameter of 31 mm, 11 days before the LH peak, and it was still present 7 days later (28 mm). An abnormal pattern of follicular growth had therefore been re-established.

The patient received a repeated course of treatment with EE_2 (30 μg daily) and MPA (5 mg twice daily) for 4 weeks (Fig. 5). LH and FSH levels were again suppressed, and on this occasion there was no early rise in E_2 levels. The first cycle after treatment was again monitored. FSH was high throughout the cycle as to a lesser extent was LH. Nevertheless, the overall pattern was again consistent with ovulation, although E_2 levels again failed to fall normally at the end of the cycle, suggesting that the high FSH throughout had once again prematurely stimulated the next crop of follicles. A third course of treatment with EE_2 and MPA as above, was followed by similar hormone and ultrasound findings (data not shown).

Discussion

In women approaching the menopause a series of biological changes take place including inappropriate gonadotrophin secretion and reduction of the frequency of ovulation (Sherman & Korenman 1975; Reyes *et al* 1977; Metcalf *et al.* 1981*a, b;* Metcalf & Livesey 1985). It is likely that similar changes occur preceding premature menopause, although this is poorly documented (O'Herlihy *et al.* 1980; Rebar *et al.* 1982).

Increased gonadotrophin secretion and reduced frequency of ovulation may be interdependent. Indeed in young women with regular menstrual cycles, ordered follicular growth takes place, leading to development and rupture of a single follicle from an initial cohort of about 6–30 follicles 1–15 mm in diameter in each ovary (McNatty 1982). After ovulation, luteal phase secretion of E_2 and progesterone suppresses gonadotrophins to their lowest levels of the cycle, and presumably below the threshold necessary for further growth of the next crop of follicles (Gosden 1985). At the end of the luteal phase this suppression is removed, gonadotrophin levels (especially FSH) rise and development of the next crop of follicles is stimulated. In women during the menopausal transition, the primary change is believed to be the diminishing follicle stock (Gosden 1985). This is associated with a reduction in the size of each cohort of developing follicles (Block 1952) and reduced suppression of gonadotrophins (Sherman & Korenman 1975; Reyes *et al.* 1977; Metcalf *et al.* 1981*a, b;* Metcalf & Livesey 1985). High FSH levels for prolonged periods are likely to result in disrupted and chaotic follicular growth. The coexistence of high LH levels is likely to lead to erratic luteinization of follicles without ovulation.

The possibility therefore exists that prolonged and effective suppression of gonadotrophin levels might line up the growing follicles by allowing those that have been committed by inappropriate gonadotrophin levels to regress. After a time a new crop of healthy follicles would have advanced to the appropriate stage. Discontinuation of suppression would be anticipated to result in a rebound rise of gonadotrophins which in turn might trigger normal follicular growth and ovulation, for one cycle.

In a patient whose hormone changes suggest that she is approaching a premature menopause we have examined, for the first time, a simple and novel approach to the induction of ovulation in such cases. Our results have documented apparently normal 'rebound' ovulation on three

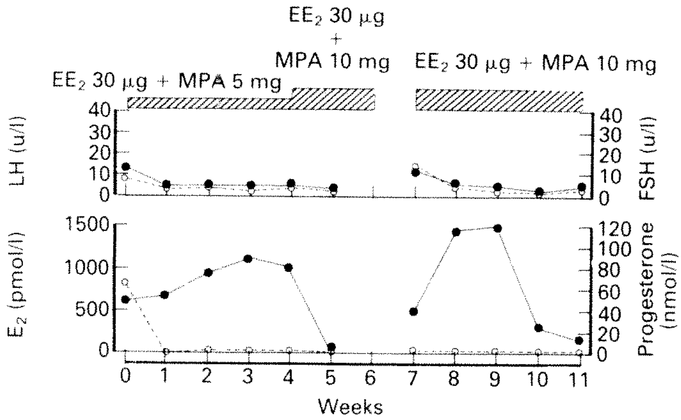

Fig. 4. Gonadotrophins and sex-steroid hormone levels during suppression treatment with ethinyl-oestradiol (EE_2) and medroxyprogesterone acetate. *Top:* (●——●) LH, (○- - - -○) FSH. *Bottom:* (●——●) E_2; (○- - - -○) progesterone.

occasions following suppression of endogenous gonadotrophins with EE_2 and MPA for a month.

The studies in three cycles over a period of 7 months showed a variable pattern. One recurrent feature was intermittent elevation of FSH. Furthermore, luteinization as evidenced by a rise in progesterone was accompanied in two cycles by very low E_2 levels, and a pattern consistent with maturation of new follicles when luteinization of earlier follicles was still evident. It is probable that under the stimulus of the inappropriately high FSH, maturation of a new crop of follicles is initiated during the luteal phase, at a time when under normal circumstances this would be impossible because of suppression of gonadotrophins to their lowest levels by circulating E_2 and progesterone. Thus the apparent follicular phase is short only because follicular growth has already commenced during the preceding luteal phase. Such a notion has not been postulated previously. If correct, it is unlikely under such disordered stimulation that normal follicular maturation would ever occur.

An interesting observation during two of the three spontaneous cycles studied (Figs 2 and 3) is that the elevated FSH levels tended to be suppressed during the pre-ovulatory and luteal phase E_2 rise, but they did not fall to levels seen in normal cycles in the corresponding stages. It would therefore appear that negative feedback

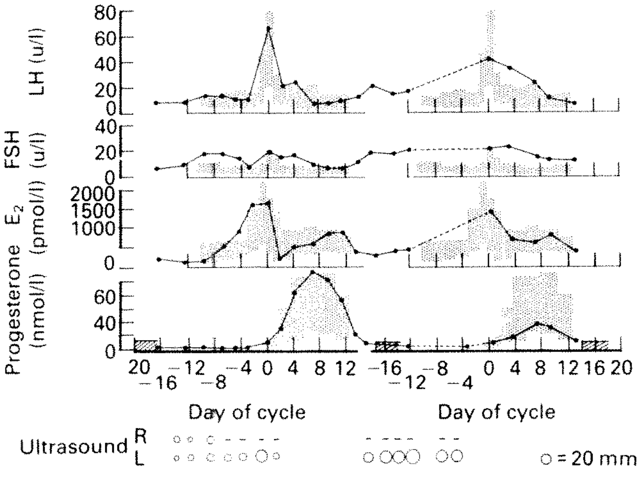

Fig. 5. Composite picture of the hormonal and ultrasound profiles of the two consecutive cycles following the suppression shown in Fig. 4.

control of gonadotrophin secretion in our patient was deranged. This finding can be explained by either a reduction in the secretion of the putative FSH-suppressive hormone inhibin (Sherman & Korenman 1975) or by a higher set-point of the hypothalamus to suppression by steroids (Metcalf & Livesey 1985).

A high degree of suppression of gonadotrophins was achieved with EE_2 and MPA. Our data suggest that 4 weeks suppression at least is necessary in order to achieve both low gonadotrophin levels and a fall in endogenous E_2 to low levels that would indicate regression of previously stimulated follicles.

The first post-treatment cycle after each of these courses of treatment was characterized by normal follicular development and ovulation as indicated ultrasonically (Figs 5 and 6). Gonadotrophin levels during both post-treatment cycles were re-established at inappropriately high levels although steroid secretion closely resembled that seen in normal cycles with the exception of resumption of menses when progesterone levels declined while E_2 levels remained high.

We postulate that the induced 'rebound' ovulation was due to synchronization of follicular growth by the end of treatment. Upon cessation we suggest that a 'healthy' crop of small antral follicles had become ready to respond to the stimulation provided by the abrupt (and excessive) rebound FSH rise. It appears that even by the end of the first cycle off treatment the pattern had returned to an abnormal one. We believe that our results indicate that induction of ovulation post-treatment was a consequence of the treatment itself and not fortuitous, since it could be reproduced after subsequent courses of treatment.

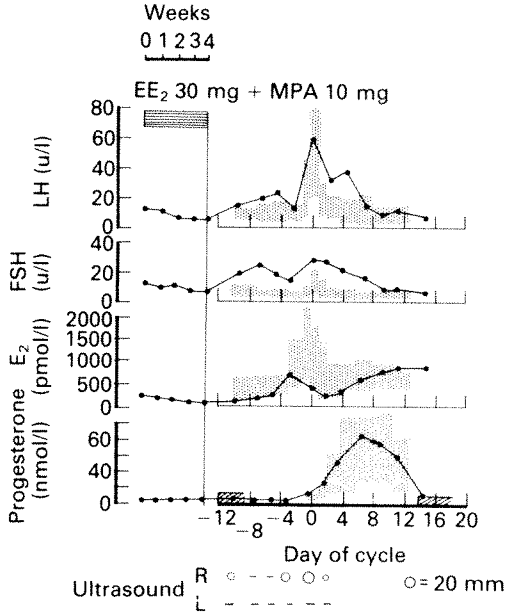

Fig. 6. Composite picture of the gonadotrophins and sex-steroid hormone levels during suppression with ethinyl-oestradiol (EE_2) and medroxyprogesterone acetate (MPA) and over the menstrual cycle following discontinuation of treatment.

Increased fertility has been reported in normal women after discontinuation of oral contraceptives (Goldzieher *et al.* 1962; Igarashi *et al.* 1965) and induction of ovulation after treatment with oestrogen and progesterone in women with anovulation of no apparent cause (Townsend *et al.* 1966). Likewise establishment of pregnancy has been reported on or after treatment with oestrogens or sequential administration of oestrogens and progestogens in women in whom a diagnosis of premature menopause has been made (Polansky & de Papp 1976; Shangold *et al.* 1977; Starup *et al.* 1978); however the hormonal changes and rationale were not well-documented. We believe that the results presented here provide evidence to substantiate such claims.

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An unusual presentation of pulmonary thromboembolism in late pregnancy. Case report

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Case report

A 22-year-old married woman, para 2 + 0, presented at 37 weeks gestation with a 5-h history of severe intermittent right hypochondrial pain. She described no gastrointestinal, urinary or respiratory symptoms and no vaginal bleeding. She was aware of good fetal activity. Her antenatal care had been uneventful.

On general examination she was distressed and her temperature was 37·3°C. Cardiovascular and respiratory system examination was unremarkable. Abdominal examination revealed mild tenderness without guarding or rebound tenderness in the right hypochondrium only. Bowel sounds were normal. The uterus was soft and not tender. The fetus had a longitudinal lie and cephalic presentation, the head was not engaged. Vaginal examination revealed an uneffaced, undilated cervix. A cardiotocographic fetal heart rate tracing was reactive.

Urinalysis was negative for protein and blood. The WBC canal was $11{\cdot}8\times10^9$/l and the haemoglobin concentration was 11·9 g/dl.

Six hours later she had developed a generalized persistent abdominal pain. On general examination her temperature was 37·8°C, pulse 116/min and blood pressure was 120/75 mmHg. Respiratory system examination was unremarkable. Abdominal examination elicited generalized tenderness and guarding with rebound tenderness. The fetal heart was present and normal and there was no vaginal bleeding.

The clinical impression was that of either acute appendicitis or a perforated viscus. Placental abruption was considered unlikely. Laparotomy failed to reveal any free fluid or blood within the peritoneal cavity. The stomach, small and large intestine, appendix, gall bladder, liver, kidneys and pancreas were normal. The uterus, both uterine tubes and ovaries appeared healthy.

A live female infant weighing 3·580 kg was born in good condition by lower segment caesarean section. Then 48 h after laparotomy, the patient described right hypochondrial and shoulder pain which was exacerbated by deep inspiration. She was normotensive but her temperature was 38·1°C, pulse 110/min and respiratory rate 36/min. Again respiratory system examination was normal and there were no signs of deep vein thrombosis. Blood gas analysis revealed her to be hypoxic (hydrogen ion 40 mmol/l, $P\mathrm{co}_2$ 5·4 kPa, arterial bicarbonate 260 mmol/l, $P\mathrm{o}_2$ 9·9 kPa).

Isotope lung scan revealed a perfusion defect in the anterior basal region of the right lung which in the absence of chest X-ray abnormality was consistent with a diagnosis of pulmonary embolism.

She was anticoagulated with intravenous heparin initially and later warfarin. Her symptoms subsided over the next few days and she was discharged home taking oral anticoagulants.

Discussion

Pulmonary thromboembolism is the leading cause of maternal death in England and Wales (DHSS 1982). The protean manifestation of this condition may present difficulty with the diagnosis; patients with pulmonary thromboembolism may present with acute abdominal pain and have no other features suggesting the diagnosis (Henderson *et al.* 1984). However, review of the literature has failed to reveal such a case presenting in pregnancy.

The main presenting feature of this case was abdominal pain. The patient described none of

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the classical symptoms and signs of pulmonary embolism (Henderson *et al.* 1972) until 48 h after laparotomy.

In view of the persisting features of an acute abdomen a laparotomy was conducted but revealed no intra-abdominal pathology, but the development of chest symptoms necessitated further investigations and a perfusion lung scan confirmed pulmonary embolism.

It seems unlikely that there was another unknown cause for the abdominal pain and that pulmonary embolism took place following laparotomy and caesarean section. It is difficult to explain the mechanism of abdominal pain in this patient, especially when it preceded other features of pulmonary infarction. Possible explanations are that it may have resulted from diaphragmatic pleurisy (Henderson *et al.* 1984) or tension on sensory nerve endings in the parietal pleura and hyperalgesia of intercostal muscles (Gorham 1961).

Heparin is the drug of choice in the treatment and prophylaxis of thromboembolic disease. There is an estimated 4–12% risk of this condition recurring in subsequent pregnancies (Badarucco & Vessey 1974; Lao *et al.* 1985). The varied manifestation of this condition must be recognized; thereby allowing early and appropriate management.

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Fetal and maternal uteroplacental leucocytes in aplastic anaemia. Case report

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Case report

A 20-year-old primigravid woman was admitted at 28 weeks gestation with a severe pancytopenia detected one week previously by a routine antenatal blood test. Her haematological status had been normal at the first antenatal visit at 9 weeks gestation. She had remained well throughout gestation apart from a chest infection treated with amoxycillin, 8 weeks before admission. There was no other recent medication other than iron and folate supplements, and no contact with known toxins. There was no evidence of hepatosplenomegaly or lymphadenopathy. Her haemoglobin was 6·6 g/dl, WBC 1·2 × 10^9/l, neutrophils 0·5 × 10^9/l, lymphocytes 0·7 × 10^9/l, platelets 7 × 10^9/l, reticulocytes 0·5%. Lymphocyte subsets were present in normal proportions: total T cells (OKT3), 91% (normal 71–95%); OKT4-positive cells, 57% (normal 37–71%); OKT8-positive cells, 24% (normal 14–58%); B cell (OKIal), 16% (normal 6–18%). Serum iron, serum vitamin B12, serum and red cell folate were normal, as was the biochemistry profile. The prothrombin and kaolin-cephalin clotting times were also normal. The bone marrow aspirate and trephine appearances were those of severe aplastic anaemia. Hams and sucrose lysis tests were negative. Serum antinuclear antibody was detected at a concentration of 100 i.u./ml with a speckled pattern, but DNA-binding was normal. No serum lymphocytotoxic antibodies were detected, and complement components C3 and C4 were in normal range with no evidence of conversion.

Fetal growth was average for gestational age as assessed by serial ultrasound measurements of biparietal diameter and abdominal circumference. The head to abdominal ratio was normal. Cardiotocography showed a normal trace. For the remainder of the pregnancy the patient received 15 units of blood to maintain her haemoglobin above 9 g/dl. Platelet transfusions were given when there was evidence of bleeding. A total of 92 units were required, which were irradiated before transfusion as were all other blood products. She had several severe septicaemic episodes, successfully treated with broad-spectrum antibiotics. Labour was induced at 36 weeks and a healthy 2.32 kg male baby was born vaginally. Cord blood haemoglobin was 19·3 g/dl, WBC 13·0 × 10^9/l, lymphocytes 9·3 × 10^9/l, neutrophils 3·0 × 10^9/l, eosinophils 0·7 × 10^9/l, and platelets 150 × 10^9/l.

Macroscopically the placenta (325 g) showed patchy calcification and extensive fibrosis. Fresh frozen sections of villous placenta and reflected amniochorion (including amniotic epithelium, amniotic mesenchyme, chorion laeve and decidua parietalis) were stained by an indirect immunoperoxidase technique with monoclonal antibodies directed against the leucocyte-common antigen (LCA) (F-10-89-4), a monomorphic determinant of class II MHC products including HLA-DR (CR3/43), tissue macrophages (anti-leu-M3) and T lymphocytes (UCHT1 and DAKO-T2) (Bulmer & Sunderland 1984; Bulmer & Johnson 1984, 1985). Fetal macrophages reactive for LCA (a marker of bone marrow-derived leucocytic cells),

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HLA-DR and leu-M3 were identified in normal numbers in the amniotic mesenchyme (Fig. 1). Normal numbers of anti-leu-M3-positive fetal macrophages were also noted in the chorionic villous stroma. Substantial numbers of T lymphocytes were identified with UCHT1 and DAKO-T2 in decidua parietalis, but the majority of maternal LCA-positive cells at this site were macrophages which expressed both HLA-DR and the leu-M3 macrophage antigen (Fig. 1). The total number of both lymphocytes and macrophages was comparable with that seen in normal third-trimester decidua.

Following delivery, there was no significant change in either the mother's or the baby's haematological status. A search to find a suitable HLA-compatible bone marrow donor for the mother was unsuccessful. One month after delivery the patient remained severely aplastic and a course of antithymocyte globulin (ATG) was given. She obtained a partial response, with an increase in the neutrophil count to 0·8 × 10^9/l, but with no increase in platelet count which remained less than 10 × 10^9/l. A second course of antithymocyte globulin had no further effect. She continued to require fortnightly blood transfusions and platelet support was given when she had clinical evidence of bleeding. However, despite this, she developed a cerebral haemorrhage and died 8 months after delivery.

Discussion

Recent immunological interest in successful semi-allogeneic human pregnancy has focused on local immune responses in the uterus and its contents (Clark 1985). Immunohistochemical techniques have been applied to uteroplacental tissues to characterize immunocompetent cells which may be essential to normal local materno-fetal immunological interactions (Bulmer & Sunderland 1984; Bulmer & Johnson 1984, 1985). Fetal macrophages have been identified in the chorionic villous stroma and amniotic mesenchyme throughout gestation (Sutton *et al.* 1983; Bulmer & Johnson 1984). Leucocytes are also abundant in maternal decidua (Bulmer & Sunderland 1984; Kabawat *et al.* 1985). The majority are macrophages but an additional large population of unusual T lineage lympho-

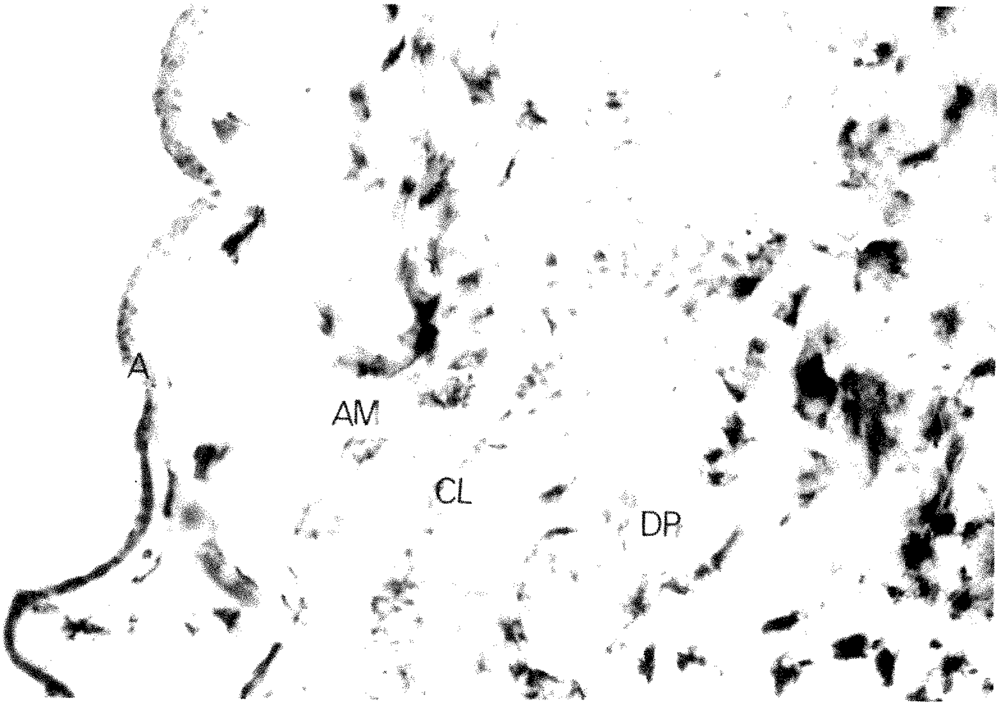

Fig. 1. Frozen section of reflected amniochorion stained in an indirect immunoperoxidase technique with a monoclonal antibody (CR3.43) recognizing HLA-DR locus products. Note both positive maternal cells in the decidua parietalis as well as fetal cells in the amniotic mesenchyme × 128. A, Amniotic epithelium; AM, amniotic mesenchyme; CL, chorion laeve; DP, decidua parietalis.

cytes have been identified in the first-trimester (Bulmer & Sunderland 1984; Bulmer & Johnson 1984). The origin and differentiation of these decidual leucocytes is not yet known.

In the present patient, although the maternal leucocyte count was low, a normal distribution and a number of leucocytes were clearly identified in decidualized endometrium. This probably indicates that these leucocytes are recruited into endometrium in early pregnancy or during the menstrual cycle and thereafter divide and differentiate *in situ*. Alternatively, bone marrow-derived cells may be recruited preferentially into decidua throughout pregnancy either as mature populations or as immature precursors which undergo further differentiation and maturation in the pregnant uterus. The generalized pancytopenia noted in this patient appears to have had no effect on local cellular materno-fetal immunological interactions in uteroplacental tissues.

Aplastic anaemia occurring in pregnancy is an uncommon event. Although previously associated with an extremely poor prognosis (Fleming 1973), cases reported since 1970 have been associated with an overall maternal survival of 80% (Suda *et al.* 1978). The survival rates, however, are proportional to the severity of the aplasia. Infection remains the most common cause of mortality. Although generalized bleeding is a major complication, there have been no reported cases of death due to uncontrollable obstetric bleeding since 1952. The optimal management appears to be support of the patient until vaginal delivery of a viable infant can be achieved using synergistic combinations of broad-spectrum antibiotic, blood transfusions and platelet transfusions when there is evidence of bleeding. Resistance to platelet transfusions has been overcome in some cases by the use of HLA-matched platelets (Goldstein & Coller 1975).

We are unaware of any substantive reports of ATG being given during pregnancy. Since we appeared to be successfully supporting the mother with blood products and antibiotics, we were reluctant to give ATG before delivery for three reasons. ATG is often associated with severe hypersensitivity reactions (Champlin *et al.* 1983) the management of which would potentially be more dangerous during pregnancy. Secondly, the effect of ATG on the complex immunological interactions of pregnancy is unknown. Finally, spontaneous recovery from aplastic anaemia following delivery has been reported in eight patients (Fleming 1973). This has usually been in the immediate few weeks post-partum. Three of these women have relapsed during subsequent pregnancies suggesting that the pathogenesis of the aplastic anaemia may be directly related to the pregnancy, perhaps involving an abnormality of the microenvironment rather than an abnormality of the stem cell population.

In conclusion, this case demonstrates that the decidualized endometrium contains a normal distribution and number of leucocytes even in the setting of severe maternal leucopenia.

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Haemangioma of the ovary with associated endometrial hyperplasia. Case report

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Case report

In 1981, a 59-year-old woman was investigated for heavy postmenopausal bleeding in the preceding 7 weeks. Her only other complaints were of an aching sensation in both breasts and occasional migraine-type headaches. The menopause had occurred 6 years previously, up to which time her menstrual cycle had been regular 6/28 days with heavy bleeding and dysmenorrhoea. She was para 2 + 0 and had no significant past medical history.

On examination she was obese and had a bulky 12-week size uterus.

A dilatation and curettage was performed. The curettings were polypoidal and microscopically showed cystic glandular hyperplasia (Fig. 1). Three months later total hysterectomy and bilateral salphingo-oophorectomy were performed with an uneventful postoperative recovery. She remains well at the time of writing.

The operative specimen consisted of a uterus and cervix 9 × 6·5 × 4·5 cm with attached fallopian tubes and ovaries, each measuring 2 × 2 × 1 cm.

Histological examination showed cystic glandular hyperplasia in the endometrium and foci of adenomyosis in the myometrium. The cervix and fallopian tubes were unremarkable. The left ovary contained a small focus of endometriosis. The cortex of the right ovary contained a well-circumscribed mixed capillary and cavernous haemangioma 1·5 cm in diameter (Fig. 2). The vascular spaces were lined by a single layer of regular endothelial cells and separated by fibrous tissue. The surrounding ovarian stroma was luteinized (Fig. 3).

Discussion

Haemangioma of the ovary is a rare lesion, with reviewers (Fox & Langley 1976; Blaustein 1982) accepting less than 30 cases in the literature. This is, perhaps, surprising in view of the vascularity of the ovary. Ovarian haemangiomas have been described over a wide age range from 4 months to 63 years. They are usually incidental findings, but have presented with abdominal pain, palpable abdominal masses and with ascites. Although usually unilateral, occasional bilateral examples have been described and also ovarian involvement in patients with generalized haemangiomatosis. Simple oophorectomy is curative.

Stromal hyperplasia with luteinized enzymatically active stromal cells has now been well described in association with many non-endocrine ovarian tumours, particularly mucinous neoplasms and Brenner's tumours (Morris & Scully 1958; de Brux & Gautray 1984). The explanation for this phenomenon is uncertain.

Whilst there are many descriptions of stromal hyperplasia, accompanying epithelial tumours, it is much more rarely described with non-epithelial neoplasms.

Several authors (Ming & Goldman 1962; Fox 1965) have described evidence of endometrial stimulation in association with ovarian neoplasms accompanied by stromal hyperplasia but, to our knowledge, none have described this in relation to a capillary haemangioma.

Cystic glandular hyperplasia is usually the result of prolonged unopposed oestrogen stimulation of the endometrium. In our post-

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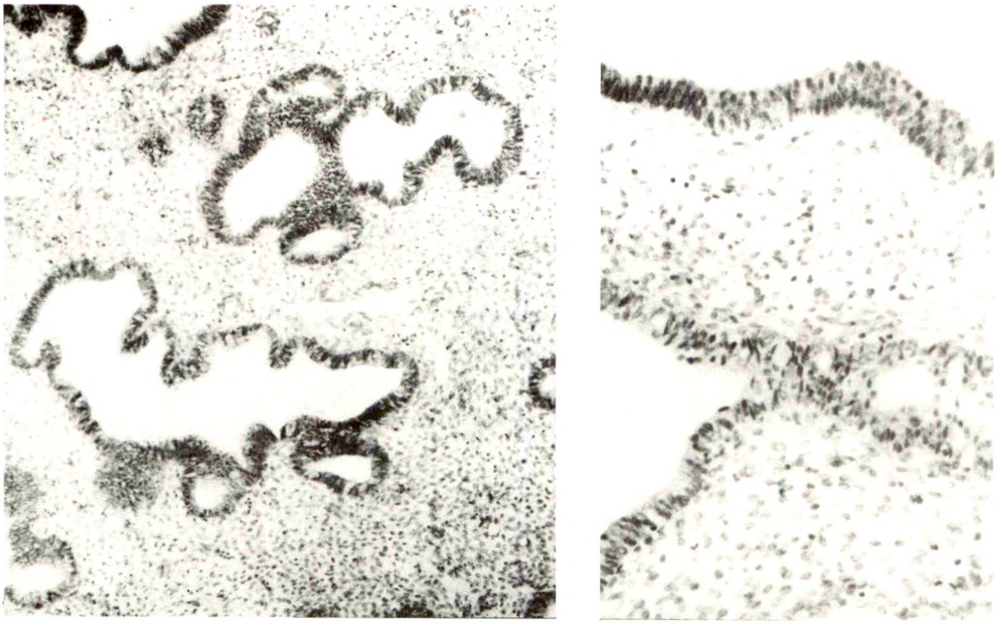

Fig. 1. Endometrium — cystic glandular hyperplasia. Dilated glands lined by a stratified mitotically active epithelium. (Haematoxylin and eosin (*left*) × 80, (*right*) × 200).

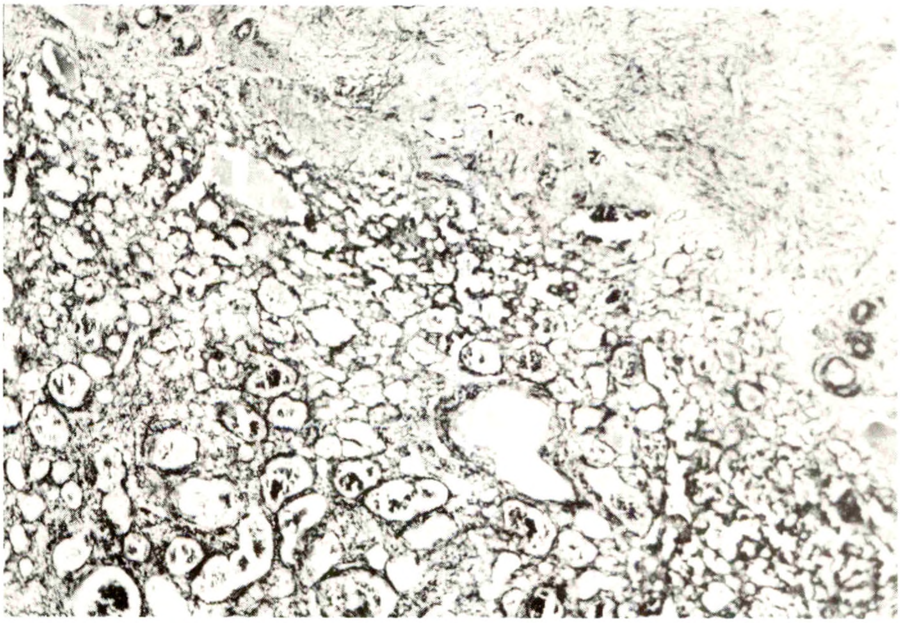

Fig. 2. Ovary — haemangioma. Numerous vascular spaces of varying calibre with adjacent ovarian stroma, top right. (Reticulin × 70).

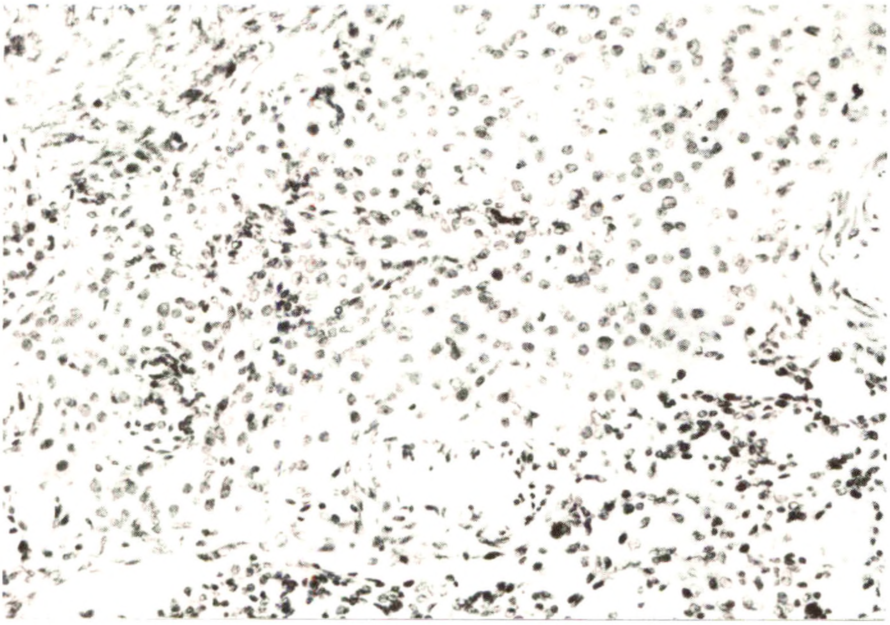

Fig. 3. Ovary — luteinized stroma. Top left, ovarian stroma. Centre, band of large luteinized stromal cells. Bottom right, haemangioma. (Haematoxylin and eosin × 200).

menopausal patient, who was not receiving exogenous steroids, an oestrogen secreting ovarian tumour is the most likely explanation for her endometrial hyperplasia.

In view of her obesity, however, an alternative explanation might be that there was an increased peripheral conversion of androgens which may, or may not, have been produced by the luteinized stromal cells within the ovary containing the haemangioma (MacDonald *et al.* 1978).

We believe this to be the first account of stromal luteinization accompanying an ovarian haemangioma and also the first account of this lesion, presenting with postmenopausal bleeding, having probably stimulated endometrial hyperplasia.

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Ovarian metastasis from stage 1B squamous carcinoma of the cervix. Case report

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Case report

The patient, a 30-year-old woman who had never been pregnant, was initially referred because of a clinically suspicious cervix in association with backache. There was no menstrual irregularity. The initial cervical smear by the family practitioner was reported as normal.

Colposcopic examination revealed an overt central carcinoma involving all four quadrants with raised irregular epithelium and abnormal vessels. The lesion was confined to the cervix but extended into the endocervical canal. The uterus was small and mobile. The adnexae were clear. Rectal examination was negative. Generous punch biopsies were taken. Histology was reported as moderately well-differentiated squamous carcinoma of cervix. Intravenous pyelography, chest X-ray, urinalysis and biochemical and haematological indices were normal.

Modified Wertheim's hysterectomy was performed 2 weeks later with bilateral pelvic node dissection. The left ovary contained a small corpus luteum and was removed. The right ovary which appeared normal was conserved. There were no palpable para-aortic nodes and the liver was smooth and of normal size.

The patient made an excellent postoperative recovery complicated only by a urinary tract infection. She went home on the 8th postoperative day.

Pathological findings

Sections of the cervix showed an infiltrating, poorly-differentiated squamous carcinoma confined to the cervix. The resection margins of the vaginal cuff were free of tumour. Uterus and ovary were normal. No tumour was seen in any of the lymph nodes.

Progress

Initial psychosexual problems complicated her recovery but she remained physically well for 13 months. Thereafter she complained of vague right iliac fossa pain and backache. Pelvic and abdominal examination were unremarkable. The vaginal vault smears were normal. Urinalysis was negative.

Sixteen months postoperatively the abdominal discomfort had resolved but backache persisted. At this time there was slight tenderness over the right sacro-iliac joint. Vaginal examination revealed a small 0·5 cm^2 nodule at the centre of the vault. Smears were again negative. Computerized tomography (CT) showed local thickening of the bladder wall but was otherwise normal. The tenderness persisted and an ultrasound scan 2 months later revealed a 5·6-cm echodense mass above and to the right of the vaginal vault.

Laparotomy was performed and the right ovary was found to contain a 5-cm semi-solid cyst. The ovary was mobile. Small irregular nodules were found on the rectal serosa and pelvic peritoneum.

The ovary was removed along with all detectable tumour nodules. Omentectomy was carried out. The liver was normal and no diaphragmatic abnormality was found.

The patient recovered well from her second laparotomy. Histology showed poorly-differentiated squamous carcinoma in the ovary and peritoneal nodules. Electron microscopy was consistent with a poorly-differentiated squamous carcinoma. The omentum was tumour free and peritoneal washings were negative.

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Postoperatively 4500 cGy external radiation therapy was given to the pelvis (20 fractions).

Nine months later the patient remains well. Clinical examination, sonar and CT scans, pelvis and lumbar spine X-rays and vault smears were normal.

Discussion

In order to avoid the effects of castration on the younger woman radical hysterectomy with conservation of one or both ovaries has become an accepted method of treatment of early carcinoma of the cervix.

This conservative approach to the surgery of cervical carcinoma was pioneered by McCall *et al.* (1958) who were unable to find a case of ovarian metastases in any lesion less than stage III. These findings were confirmed by Yagi (1955) in a series of 500 surgical cases of squamous carcinoma of the cervix and in a smaller series from Webb (1975) in California. Spread of cervical carcinoma to the ovary is therefore rare. A search of the literature has revealed only two reported clinical cases (Nahhas *et al.* 1977; Johnston & Clausen 1982). The first was diagnosed in pregnancy. The patient had a stage 1B carcinoma of cervix with spread to an ovarian endometrioma. The second case was clinically stage 1B but there was bilateral pelvic node involvement at surgical resection.

Several authors have performed extensive post-mortem examination to identify ovarian metastases in patients with carcinoma of the cervix. In a total of 1140 patients there were only four with ovarian metastasis of whom three had endometrial spread. (Baltzer *et al.* 1981; Behney 1933; Brunschwig & Pierce 1948; Hendriksen 1949; Nicolescu 1964).

Preservation of ovarian function is one of the most forceful arguments for surgical treatment of cervical carcinoma as opposed to radiation therapy in the young woman. Ovarian spread from cervical cancer does occur, albeit rarely.

With the knowledge that adequate hormone replacement therapy is easily available, clinicians faced with such cases should consider carefully the advisability of ovarian conservation in young women with malignant disease of the cervix.

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A feminizing Sertoli–Leydig cell tumour in a postmenopausal woman. Case report

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Case report

In November 1984 a 73-year-old woman, para 4+1, attended for routine examination. She had her last menstrual period at the age of 58 and underwent a curettage for postmenopausal bleeding 5 years later; an endometrial mucous polyp was removed and the endometrium was found to be atrophic. She was given oestrogen replacement therapy (oestriol 2 mg per day) until the age of 68.

She was in good general health, body weight 55 kg, height 159 cm, and there were no signs of virilization. The vaginal mucosa was well-oestrogenized as illustrated by the dominance of superficial and intermediate cells in the vaginal smear. A left-sided mobile, solid adnexal mass, the size of an orange, was found on pelvic examination and this was confirmed by echography. Serum concentrations of luteinizing hormone and follicle stimulating hormone were 33·6 m-i.u./ml and 11·0 m-i.u./ml; the concentration of oestradiol (E_2) was 0·65 nmol/l and of testosterone (T) 2·26 nmol/l. Haemoglobin and haematocrit values were normal. A uterine curettage was performed because the patient had experienced some vaginal bleeding a few days after the first visit. The endometrium showed signs of cystic glandular hyperplasia. The presence of a left-sided ovarian tumour was confirmed at laparotomy; it was semicystic, 6 × 5 × 4 cm, well encapsulated and not adherent to any of the surrounding structures. The uterus and the right ovary were normal. Blood samples for determination of gonadotrophins and steroids were taken during the operation from a peripheral vein and from both the left and right ovarian veins. A cyst in the tumour contained 13 ml clear yellowish fluid, which was aspirated for steroid analysis. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. A search for distal metastases by chest-radiography, bone scanning with ^{99m}Tc-MDP, abdominal echography and liver function tests were all negative. Further blood samples for determination of gonadotrophins and steroids were obtained at 9 and 24 days and 7 weeks after the operation. Urine was collected over a 24-h period before operation and 9 days after operation for assay of urinary oestrogens. The patient left the hospital on the 11th postoperative day and is well 5 months later.

Laboratory investigations

Hormone assays

Serum concentrations of luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured by commercial kits (Amersham International, UK) and are expressed as m-i.u./ml of the 2nd IRP of hMG. Pregnenolone (Pe), 17-hydroxypregnenolone (17-Pe), 17-hydroxyprogesterone (17-Po), progesterone (Po), dehydroepiandrosterone (DHEA), androstenedione (Adione), testosterone (T), oestradiol-17β (E_2) and oestrone (E_1) were quantitated by previously described methods (Vermeulen & Verdonck 1976). Urinary oestrogens were measured by a fluorimetric method (Eechaute & Demeester 1965). Analysis of steroids in the cystic fluid used capillary gas chromatography (Vanluchene *et al.* 1983).

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The peripheral and ovarian venous concentrations of E_2, Adione and T were measured in a comparison group of eight postmenopausal women who underwent pelvic surgery for benign gynaecological conditions without overt signs of endocrine ovarian activity. The median age was 56 years (range 53–72 years) and the median time elapsed since the menopause was 12 years (range 3–33 years).

The concentrations of LH, FSH, E_2, Po, T, Adione and DHEAS before operation, during the operation and 9 days, 24 days and 7 weeks following the removal of the tumour are given in Table 1. The basal levels of LH and FSH were comparable to those found in the midfollicular phase in premenopausal women. The peripheral level of E_2 was above the ranges found in the comparison group of eight postmenopausal patients (Table 2), while the concentrations T and Adione reached the upper limit of that range. A decline of E_2 and T and a rise of the gonadotrophins to the expected postmenopausal levels occurred after the operation. The peripheral and ovarian venous levels of the steroids at operation and the hormonal content of the cystic compartment of the tumour are given in Table 2. For lack of sufficient serum, Pe, 17-Pe, DHEA and 17-Po could not be determined in peripheral blood and the right ovarian vein. As reference, a published range of concentrations in peripheral blood in postmenopausal women is given (Abraham & Maroulis 1975). Based on the gradients between ovarian and venous peripheral concentrations, there was obvious secretion by the tumour of 17-Pe, 17-Po, DHEA, T, Adione and E_2. The ratios between the left ovarian venous concentration of the patient and the mean ovarian venous concentrations of the comparison group for E_2, T and Adione were 25·3, 8·7 and 2·9, respectively, demonstrating the biologically dominant secretion of oestradiol by this tumour.

Histology

Ovaries. The left ovary measured 6 × 5 × 4 cm. A firm white tumour was present with cysts in its periphery. The right ovary had a normal appearance with a diameter of 3 cm. On microscopic examination the tumour in the left ovary consisted mainly of closely packed spindle-shaped Sertoli cells arranged in trabeculae, sheets or cords, lying in mesenchymal stroma. Only a minor proportion of the tumour showed a tubular arrangement (Fig. 1). The tumour cells had an irregular oval nucleus with fine chromatin pattern and a distinct nucleolus. Numerous mitotic figures were present (5–8 mit/10 HPF) (Fig. 2a). A fat stain was positive in the Sertoli cells (Fig. 2b). Only very focal areas of Leydig cells were observed. The diagnosis was made of a Sertoli-Leydig cell tumour of the intermediate type.

Uterus. The uterus had a symmetrical configuration and was not enlarged. In the myometrial wall a small leiomyoma was present. The endometrium had a thickness of about 0·9 cm. In the well-developed endometrium the glands were hyperplastic with cystic dilatations. Focal areas of atypical adenomatous hyperplasia could be distinguished. These glands were covered by a tall cylindrical pseudostratified epithelium with some mitotic figures.

Discussion

Sertoli–Leydig cell tumours are rare ovarian neoplasms which account for less than 1% of all ovarian tumours (Genton 1982). They occur

Table 1. Serum levels of gonadotrophins, steroids and urinary oestrogens in a postmenopausal woman with a Sertoli–Leydig cell tumour, before, during and after operation.

Steroid	Before operation	During operation	After operation 9 days	 24 days	 7 weeks
Luteinizing hormone (m-i.u./ml)	33·6	15·8	18·9	51·1	89·6
Follicle stimulating hormone (m-i.u./ml)	11·0	6·2	22·0	125·5	94·3
Oestradiol-17β (nmol/l)	0·65	0·71	<0·04	<0·08	<0·04
Progesterone (nmol/l)	<3	<3	<3	<3	<3
Testosterone (nmol/l)	2·26	2·26	0·45	0·76	0·42
Androstenedione (nmol/l)	—	4·20	2·60	2·66	2·34
Dehydroepiandrosterone (µmol/l)	—	1·55	1·68	2·17	2·01
Urinary oestrogens (nmol/24 h)	65	—	7	—	—

Table 2. Steroid levels in peripheral and ovarian venous blood and in cyst fluid from a postmenopausal woman with a left-sided Sertoli–Leydig cell tumour compared with mean (range) levels in eight postmenopausal women (comparison group). All concentrations are expressed as nmol/l.

	Patient				Comparison group ($n = 8$)		Post-menopausal serum reference values*
Steroid	Peripheral	Left ovarian vein	Cyst fluid	Right ovarian vein	Peripheral	Ovarian vein	
Pregnenolone	—	10·5	47·5	—	—	—	8·7
17-Hydroxypregnenolone	—	21	≤3	—	—	—	1·4
Dehydroepiandrosterone	—	66	555	—	—	—	6·3
Progesterone	<3	<3	<3	<3	—	—	<3
17-Hydroxyprogesterone	—	16·5	124	—	—	—	0·7
Androstenedione	4·2	25·3	273	6·6	2·6 (0·66–4·3)	8·8 (1·4–18·2)	—
Testosterone	2·3	29	10	4·5	1·6 (0·5–2·6)	3·3 (0·6–7·2)	—
Oestrone	0·18	0·50	—	—	—	—	—
Oestradiol-17β	0·63	7·15	52	0·60	0·08 (0·04–0·10)	0·28 (0·07–1·29)	—

* Data from Abraham & Maroulis (1975).

mostly in young women who usually, but not necessarily, become virilized (Genton 1982; O'Hern *et al.* 1962). The occurrence in women older than 70 years has been reported in only three cases (O'Hern 1962; Genton 1978). Sertoli-Leydig cell tumours contain Sertoli and/or Leydig cells in varying proportions and varying degrees of differentiation. The degree of differentiation is the basis for a further classification as proposed by Meyer (1931). In the well-differentiated tumours clearly defined tubules are present, lined by Sertoli cells. These cells are separated from each other by variable numbers of Leydig cells. In the intermediate group, Sertoli cells are arranged in islands, trabeculae, sheets or chords and a tubular pattern can occasionally be observed. The Leydig cells are found singly or in groups. In the poorly differentiated group, the tumour consists mainly of closely packed spindle-shaped cells, resembling the stroma of an undifferentiated gonad. A fourth category, which is composed of Sertoli–Leydig cell tumours containing heterologous elements (mucinous cysts, cartilage, carcinoid) was added by WHO in 1973 (Serov *et al.* 1973). The malignancy rate of Sertoli–Leydig cell tumours is dependent on the degree of differentiation; reported incidences for malignancy vary from 21% (Pedowitz & O'Brien 1960) to 6·7% (Ireland & Woodruff 1976). In general, a malignant potential should be suspected in tumours

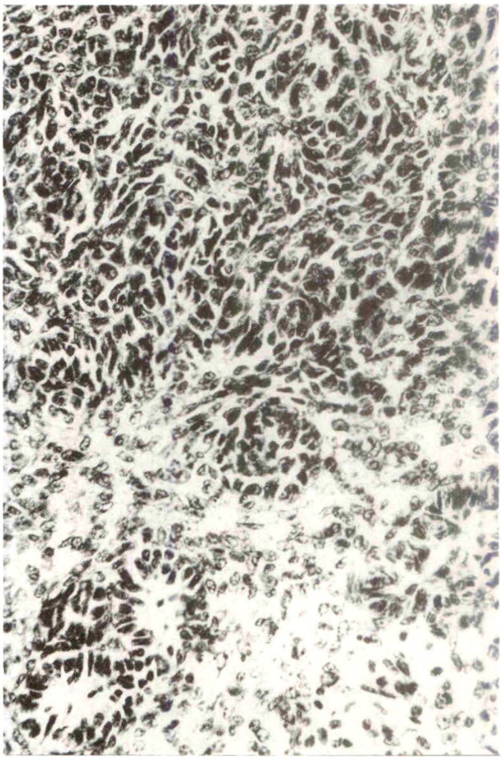

Fig. 1. Tumour consisting of closely packed spindle shaped Sertoli cells with only a minor tubular differentiation (haematoxylin and eosin ×240).

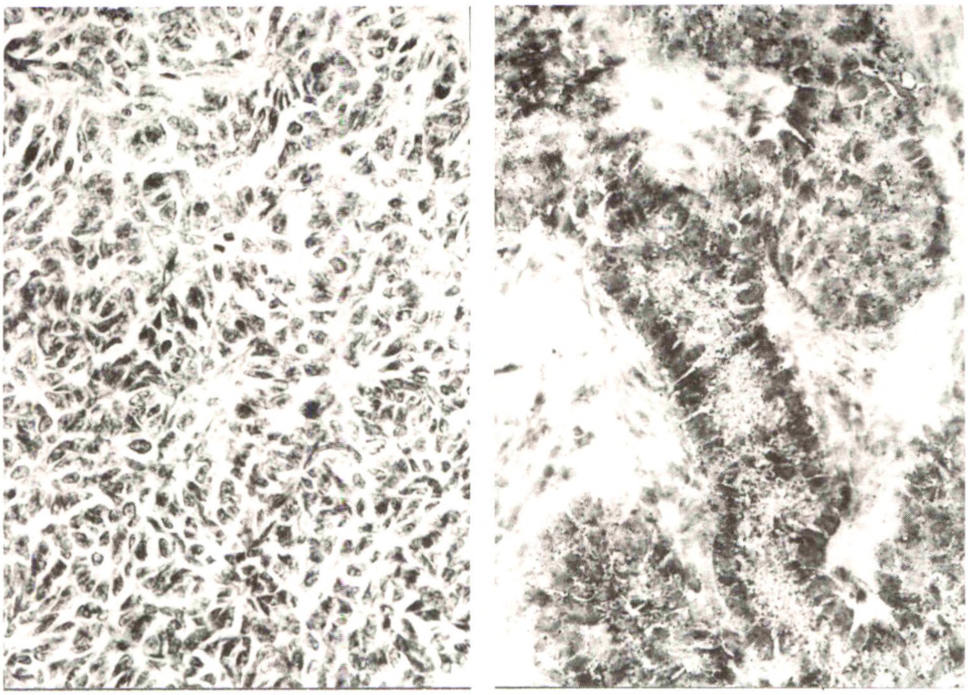

Fig. 2. (a, *left*) Tumour cells with an irregular oval nucleus and a distinct nucleolus. Some mitotic figures are present. (Haematoxylin and eosin ×300). (b, *right*) Sertoli cells showing finely dispersed fat droplets (Scharlach Red ×300).

with poor differentiation (Zaloudek & Norris 1984).

The terms arrhenoblastoma (Meyer 1931), androblastoma (Teilum 1958) and gonadal stromal tumour of android type (Genton 1980) have all been used as synonyms for the Sertoli-Leydig cell tumour. Their connotation of associated masculinization may be misleading because some of these tumours do not display an endocrine activity or may even be accompanied by feminizing manifestations. The latter effect, however, is rare; in a recent review by Shalev *et al.* (1984), only 21 cases of oestrogenizing Sertoli-Leydig cell tumours were documented. The feminizing nature of the tumour in the present case is illustrated indirectly by the effect on the endometrium and the peripheral blood levels of oestradiol and the gonadotrophins before and after the removal of the tumour. Measurement of androgens and their steroid precursors in venous blood draining ovarian tumours and the resulting biosynthetic pathways have been reported by several authors in cases of virilizing tumours. In a review of 24 cases, Meldrum & Abraham (1978) concluded that elevated peripheral androgen levels result from increased precursor supply from both the Δ_4 and Δ_5 pathway and from negligible aromatase activity. The source of oestradiol in testicular tissue is still controversial (Lipsett 1980). It appears, however, that oestradiol can be produced by the Leydig cells themselves (Valladares & Payne 1979) but may also originate from the aromatizing capacity of the Sertoli cells (Dorrington & Armstrong 1975). Pure, well-differentiated Sertoli cells tumours with few or no Leydig cells between the tubules and particularly those with lipid storage are typically associated with oestrogenic manifestations (Teilum 1958), illustrating the oestrogenic potential of Sertoli cells. Although the present tumour was of the intermediate type, the scarcity of Leydig cells and the positive fat stain of the Sertoli cells make for some similarity with this type and provide an histological explanation for its feminizing nature. As in virilizing tumours, the steroid precursor supply was derived from the Δ_4 and Δ_5 pathways, with a predominance of the Δ_5 pathway.

The appearance of virilizing or feminizing symptoms in the presence of a steroid producing tumour will ultimately depend on the T: E_2 ratio in peripheral blood (Gabrilove 1974). In normal postmenopausal women, this ratio is about 20

(Abraham & Maroulis 1975) whereas in the present case, the T:E_2 ratio was only 3·4, which favoured oestrogenic rather than androgenic effects.

The similarity of the T:E_2 ratio in the peripheral and the ovarian circulation and the considerable gradient between the concentration of oestradiol in the tumour draining ovarian vein and the peripheral blood in the present case indicate that most of the circulating oestrogens were derived from direct secretion by the tumour, presumably by virtue of the aromatizing capacity of the Sertoli cells.

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Isolated arteritis of the uterine cervix. Three case reports

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Case reports

Patient 1

A 37-year-old woman was admitted for hysterectomy because of a 4-year history of progressively worsening menorrhagia and on examination was found to have fibroids. She had two children and had been sterilized. Apart from a previous appendicectomy and excision of a cyst from the base of the spine, there was no other significant past history. There was no drug history but she was a cigarette smoker. Physical examination revealed no other abnormality.

A routine total abdominal hysterectomy was performed from which she made an uneventful recovery.

Histology confirmed a uterine leiomyoma and showed a secretory endometrium with mild chronic cervicitis. There were also several foci of arteritis within the cervix, in which there was gross destruction of the vessel wall with fibrinoid necrosis and a prominent infiltrate of mononuclear cells (Figs 1 and 2). Staining for elastic tissue revealed disruption of the internal elastic lamina (Fig. 3).

Patient 2

A 49-year-old woman was admitted for a total abdominal hysterectomy for menorrhagia. She had one child and had been sterilized 11 years previously. Apart from two previous dilatations and curettages for the present condition, there was no other significant past history and she had been taking Stelazine 2 mg daily for some years. Physical examination was normal. A routine abdominal hysterectomy was performed from which she made an uneventful recovery.

Histological examination of the resected specimen showed a secretory endometrium with mild chronic cervicitis. There was also a focus of arteritis in the cervix in which there was fibrinoid necrosis of the vessel wall and a perivascular lymphocytic infiltrate (Fig. 4).

Patient 3

A 43-year-old nullipara was admitted for abdominal hysterectomy for a several year history of progressively worsening menorrhagia and dysmenorrhoea. She was otherwise well and apart from a course of danazol for the present complaint there was no other drug history. In the past she had undergone a patellectomy for chondromalacia patellae and excision of a benign intradermal naevus on the vulva. Physical examination was normal. A routine abdominal hysterectomy was performed and at operation two small extramural fundal fibroids were noted.

Histology revealed early secretory changes in the endometrium, mild chronic cervicitis, a benign endometrial polyp and confirmed benign leiomyomata. Several small foci of arteritis in the cervix were also present, in which there was fibrinoid necrosis of the vessel wall and a prominent infiltrate of lymphocytes (Fig. 5). Special stains revealed the internal elastic lamina to be almost destroyed. (Fig. 6).

Discussion

Isolated focal arteritis is a rare occurrence but has been reported in a number of organs including cervix (Crow & McWhinney 1979), gall bladder (Bohrod & Bodon 1970), caecum (Meyer & Lichtenstein 1982), epididymis (Womack & Ansell 1985), breast (Chaitin *et al.* 1981), appendix (Plaut 1951), brain (Cupps *et al.* 1983; Bettoni *et al.* 1984; Farine *et al.* 1984; Snyder &

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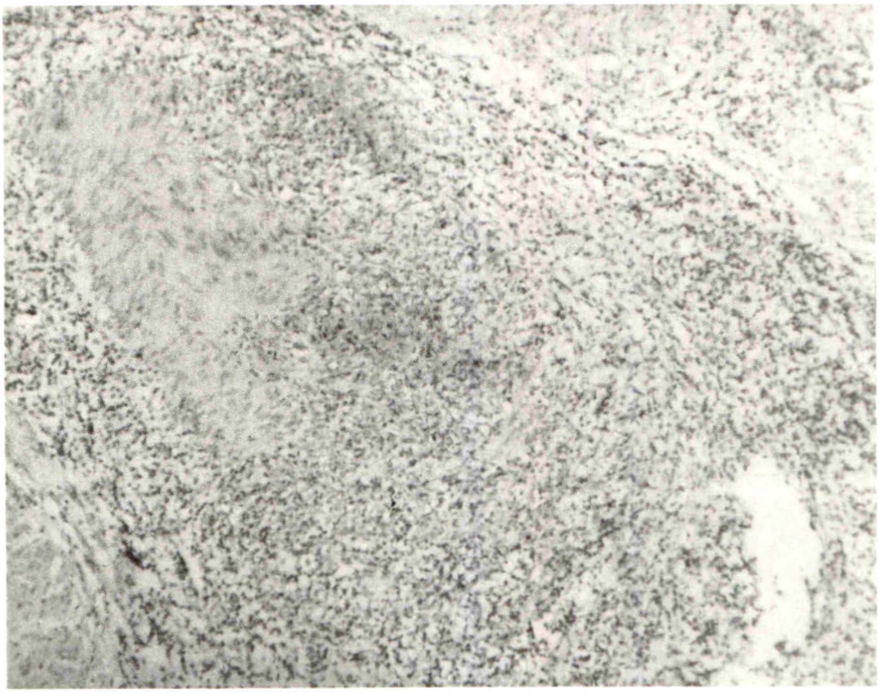

Fig. 1. Necrotizing vasculitis with destruction of the vessel wall and a prominent mononuclear infiltrate (haematoxylin and eosin × 160).

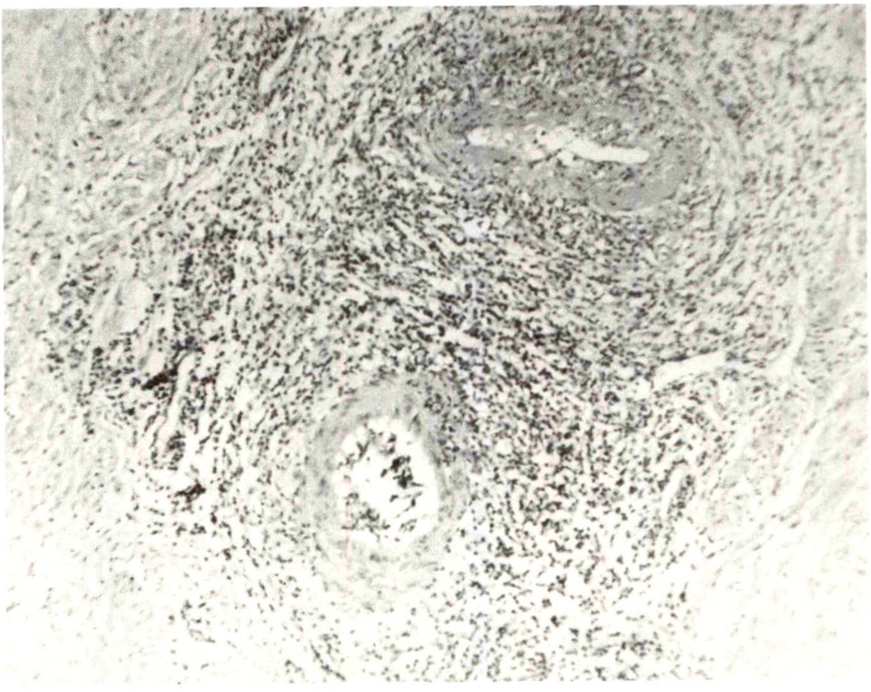

Fig. 2. Perivascular mononuclear infiltrate with fibrinoid necrosis of vessel wall (haematoxylin and eosin × 160).

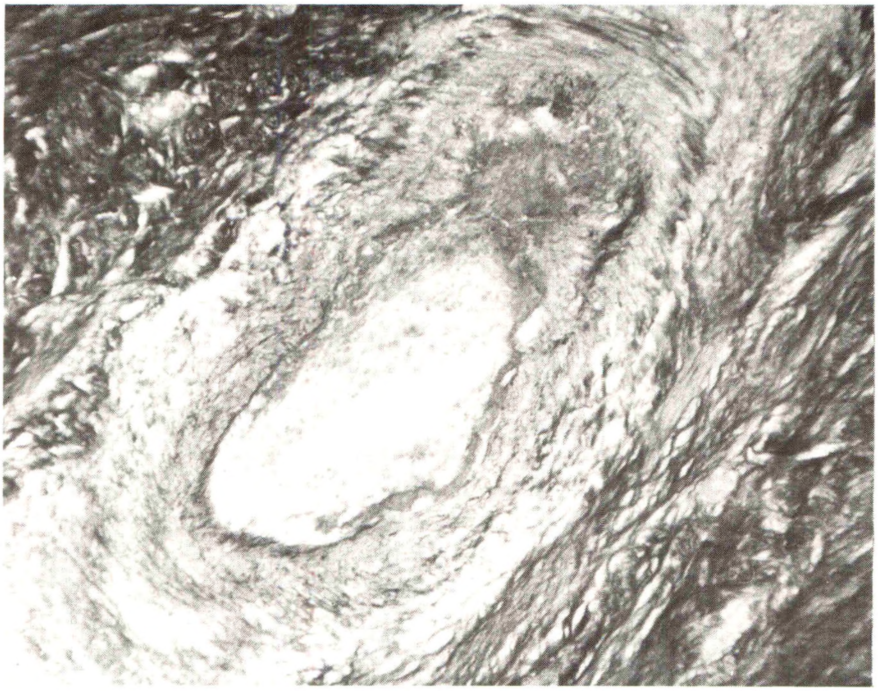

Fig. 3. Elastic stain showing damage to internal elastic lamina (haematoxylin Van Gieson × 144).

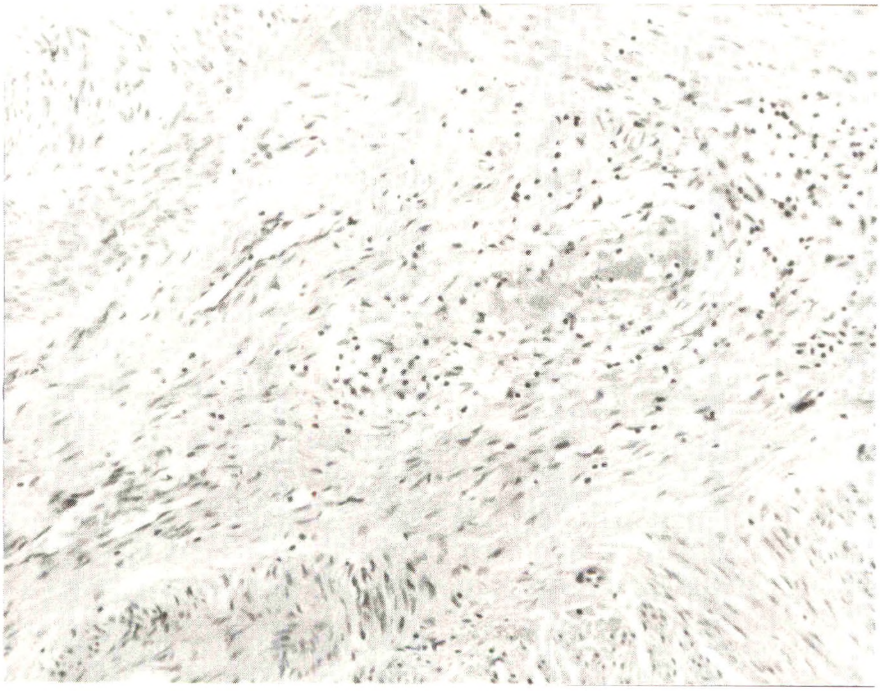

Fig. 4. Focal arteritis with perivascular lymphocytic infiltrate (haematoxylin and eosin × 160).

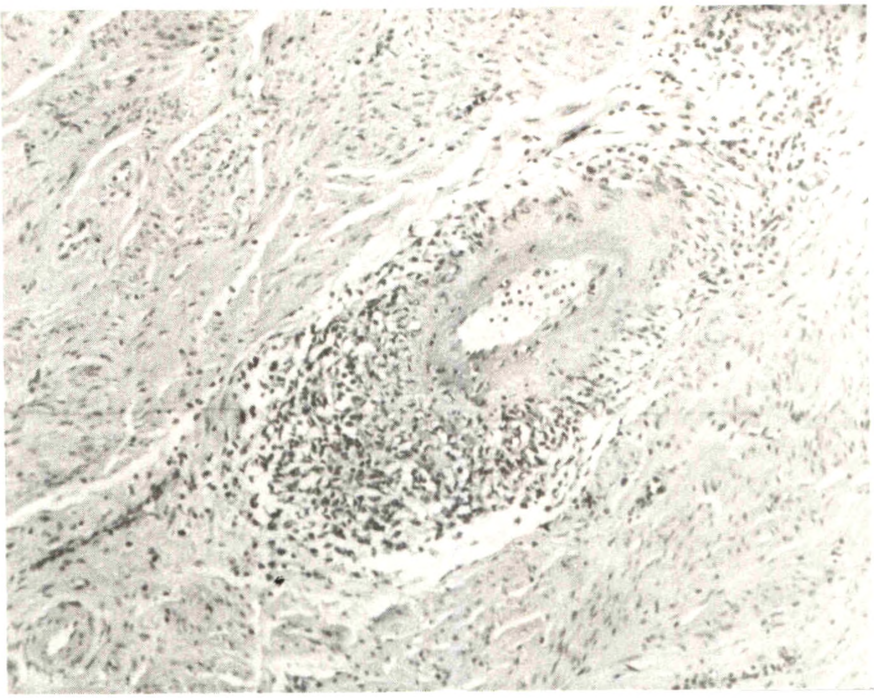

Fig. 5. Vasculitis with fibrinoid necrosis and a prominent lymphocytic infiltrate (haematoxylin and eosin × 200).

Fig. 6. Elastic stain showing almost total destruction of internal elastic lamina in two small vessels surrounded by lymphocytic infiltrate. A normal vessel at the edge of the field is present for comparison showing prominent intact elastin (orcein × 240).

McClelland 1978), spinal cord (Feasby *et al.* 1975) and coronary arteries (Ahronheim 1977). In some cases the arteritides described have been completely asymptomatic, in others local symptoms have been produced.

Polyarteritis nodosa is a generalized condition producing a necrotizing arteritis similar to that described in my patients in small and medium sized vessels throughout the body involving many organ systems and consequently producing a varied but invariably severe clinical picture. The finding of arteritis with fibrinoid necrosis has in the past been regarded as an indication of a possible generalized disease with all its connotations, and Kinn & Hedenborg (1977) described a patient, who eventually died of renal involvement, initially presenting with a lesion localized to the penis. However, their patient presented with ischaemic changes to the glans and was therefore not symptomless *ab initio* as were the women described here.

Ansell *et al.* (1974) and Wilansky *et al.* (1980) reviewed 10 and 11 cases respectively of symptomless necrotizing arteritis of the uterine cervix discovered incidentally on routine histological examination of resected specimens, and in no instance was there evidence of systemic vascular disease. This is in spite of the fact that in polyarteritis nodosa uterine lesions are not uncommon and Patalano & Sommers (1961) found uterine lesions in six of 17 necropsied cases. The findings in the present study therefore support the view of Ansell *et al.* (1974) and Wilansky *et al.* (1980) that these lesions are innocuous and no further investigation or follow-up is needed. Patients with giant cell arteritis confined to the female genital tract with no systemic manifestations discovered on routine histology have also been described (Pirozynski 1976; Schneider 1981).

The aetiology of these lesions is by no means apparent. All three patients were normotensive with no history of cardiovascular disease and no significant drug histories. A local reaction to infection has been postulated (Crow & McWhinney 1979) but there was no real evidence to support this, and immunocytochemical studies (Crow & McWhinney 1979; Womack & Ansell 1985) have been inconclusive.

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Diploid complete hydatidiform mole, mosaic for normally fertilized cells and androgenetic homozygous cells. Case report

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Case report

A 30-year-old woman with a previous history of two first trimester spontaneous abortions and no other pregnancies presented with 16 weeks amenorrhoea but a uterine size equivalent to 26 weeks gestation. Serum human chorionic gonadotrophin (hCG) level was 311 000 i.u./l and ultrasound examination indicated the presence of hydatidiform mole. hCG levels were monitored for only 2 weeks after evacuation of the uterus (as the patient did not wish to have further investigation) but showed a decline to 620 i.u. in this time. Six months later, the patient was well but no investigations were undertaken.

Laboratory studies

Methods

The uterus was evacuated and the products were examined before fixation. Several pieces of the trophoblastic tissue were removed aseptically and minced with a sterile scalpel blade. Monolayer cultures were established in three separate culture vessels containing 85% Hams F10 medium supplemented with 15% fetal calf serum.

Histopathological examination of fixed tissue sections was carried out according to the classification of Szulman & Surti (1978).

Polymorphic chromosomal regions were identified by G, C and Q banding. For classification by Q banding, the cells were photographed and prints made at four different levels of exposure. Decisions made on examination of all four prints allowed greater confidence in classification.

Histopathology

Macroscopically the specimen consisted of numerous grape-like vesicles filled with clear fluid, together with blood clots. The total weight was 608 g. Examination of sections showed only molar tissue, consisting of numerous cystically dilated chorionic villi which were completely avascular. There was pronounced oedema of the stroma leading to formation of large cisterns within the villi. This was accompanied by haphazard trophoblastic proliferation of a moderate degree (Fig. 1). The histological appearances are thus consistent with that of a complete mole.

Cytogenetics

Cells in flasks A and B grew well and 26 metaphases were analysed by Giemsa banding from direct harvests. Only two metaphases could be analysed from flask C. Two different karyotypes were found, the first heterozygous (Fig. 2) and the second, homozygous (Fig. 3) for the paternal translocation products. The frequencies of the two karyotypic types within each culture vessel are shown in Table 1.

Karyotypic analysis after further subculture revealed only heterozygous cells and it seemed likely that these had a growth advantage in our culture system.

Examination of polymorphic markers from maternal and paternal cells, using Giemsa, centromeric and quinacrine banding, revealed recognizable markers in the polymorphic

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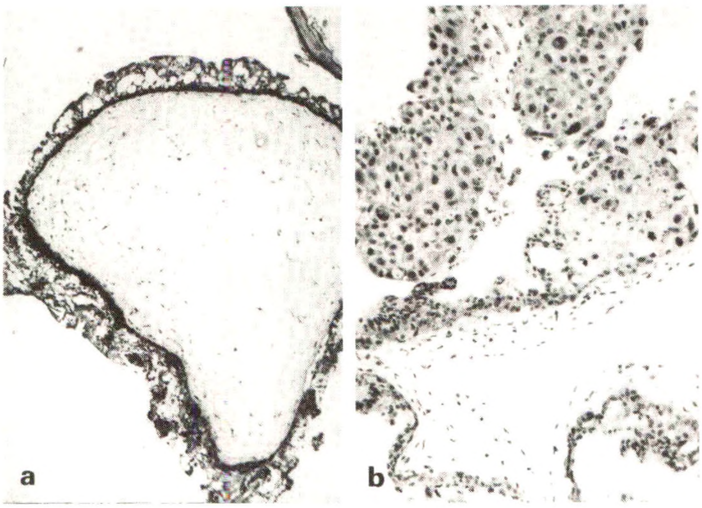

Fig. 1. (a) Cystically dilated chorionic villus with trophoblastic proliferation. Note the complete absence of blood vessels. Magnification ×40. (b) Cistern formation within dilated chorionic villus and haphazard trophoblastic proliferation. Magnification ×250.

regions of several chromosomes. The maternal complement showed a lqh+ marker which was present in the heterozygous cells and this, together with the translocation product, readily confirmed that the heterozygous cells were the product of a fusion between maternal and paternal chromosome sets (Fig. 4). Thus the heterozygous cells could be considered to be the product of a normal biparental nuclear fusion.

The cell line homozygous for the translocation products could either have been produced by fusion of two different sperm or the duplication of a single sperm. However, the paternal diploid genome was heteromorphic for markers on chromosomes 3, 13, 14, 15, 21 and 22, as outlined in Table 2, and markers on each of these chromosomes were homomorphic in the homozygous molar cell line. Thus we believe that the most likely origin of this cell line was the duplication of a single sperm. This conclusion is based on (i) absence of contrary evidence from nine cytogenetic markers (chromosomes 3, 13, 15, 15, 21 and 22, the two translocation products and the sex chromosomes), and (ii) single sperm replication is by far the more common mode of origin, being responsible for at least 90% of all complete moles (Ohama *et al.* 1981).

Where favourable markers occurred, the paternal chromosomes contributing to the heterozygous karyotype were identified and compared with those in the homozygous karyotype. Chromosomes 14 and 21 were found to be different in the two lines (Fig. 5) and, therefore, more than one sperm was involved in the determination of the two cell lines.

The presence of mosaicism in both flasks A and B implies that the mosaicism seen here reflects true mosaicism within the typically molar trophoblastic tissue.

Discussion

Hydatidiform moles are usually classified as two distinct types; namely partial and complete. The partial moles are those found in association with a fetus while no fetal development is detected in complete moles. The two types can also be distinguished by histopathological features of the trophoblast (Szulman & Surti 1978). Detailed examination of complete molar karyotypes has shown that most are homozygous and androgenetic, derived from the duplication of an X-bearing haploid sperm karyotype (Kajii & Ohama 1977). However, 5–10% of complete moles are heterozygous and androgenetic, and these are thought to be derived from the fusion of two sperm nuclei after dispermic fertilization (Ohama *et al.* 1981). Thus in both homozygous and heterozygous complete moles, the maternal chromosomes are reported to make no contribution and it is presumed that the egg nucleus is either absent (perhaps degenerating before fertilization) or is destroyed after fertilization (Jacobs *et al.* 1980).

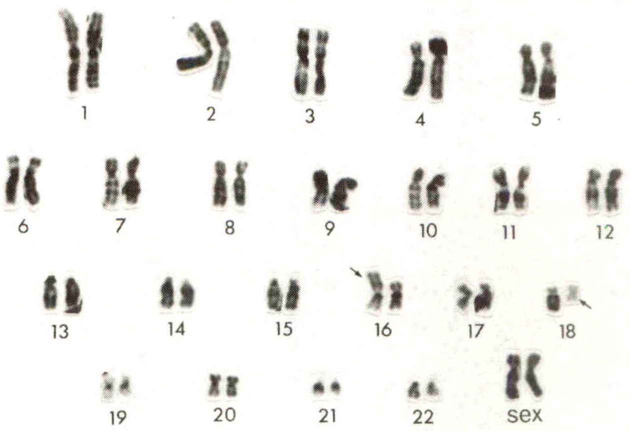

Fig. 2. Karyotype of the heterozygous molar cells. Note the translocation products (arrows).

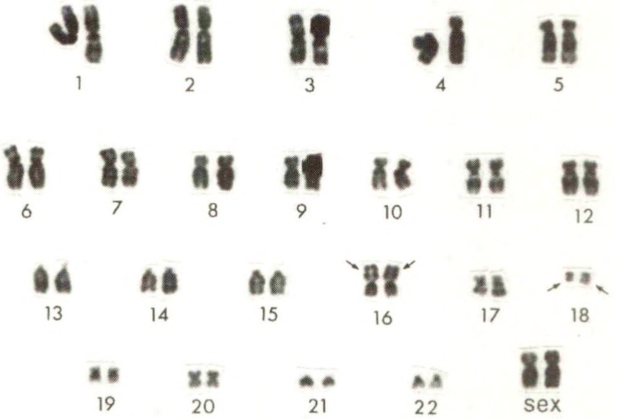

Fig. 3. Karyotype of the homozygous molar cells. Note the duplication of the translocation products (arrows).

Partial moles are usually triploid, either 69,XXX or 69,XXY. Moreover, 86% of triploid concepti are diagnosable as partial hydatiform moles (Szulman *et al.* 1981) and this group seems to correspond with those having two paternal haploid sets of chromosomes (Jacobs *et al.* 1982).

More rarely, cases of moles coexisting with normal fetuses have been reported. Karyotypic analysis of these has shown either 46,XY or 46,XX fetuses and 46,XX molar tissue. Such cases have been interpreted as dizygous twins (Fisher *et al.* 1982; Yee *et al.* 1982).

The histological features of the mole in our patient are characteristic of a complete mole. Karyotypically, however, the mole is unusual in exhibiting mosaicism for a normal biparentally derived cell line and a homozygous androgenetic cell line. Since both these lines were present in separate cultures, each established from discrete areas of the molar tissue, it seems that the two lines were derived from a single egg. The only alternative explanation requires that dizygotic twin eggs fused at such an early stage as to mimic a completely integrated mosaic conceptus. This seems unlikely but cannot be disproved.

Analysis of polymorphic markers demonstrated that two different sperm were involved in the generation of the mole, although both sperm carried the two paternal derivative translocation

Table 1. Karyotypic results

Flask	No. of metaphases		
	Heterozygous	Homozygous	Total
A	5	4	9
B	16	1	17
C	2	0	2

chromosomes. One of these sperm fused with the female pronucleus while the other duplicated in the egg cytoplasm. Dispermic fertilization in humans is relatively common. Triploidy is found in about 11% of first trimester spontaneous abortions and 80% of these are due to dispermic fertilization (Kajii & Niikawa 1977). It has been proposed that triploidy occurs more frequently in eggs which undergo delayed fertilization. However, ageing of the mother is not implicated, since triploidy is not associated with increased maternal age (Lazar *et al.* 1973). By comparison, complete molar pregnancies are greatly increased in older women (Grimes, 1984).

The characteristic feature of complete moles is the presence of a paternally-derived karyotype. In about 8% of moles this is attained by fusion of two male pronuclei following dispermic fertilization, but generally a single X-bearing sperm duplicates in the egg cytoplasm. Although many reports have proposed that this only occurs in either an empty egg or one where the egg nucleus is degenerative, the present study strongly suggests that duplication can occur in the presence of a competent egg nucleus. Further evidence for this stance is provided by data on the origin of triploidy (Kajii & Niikawa 1977). In a series of 11 cases, two triploids (both of which were in pregnancies conceived in older women) showed results consistent with duplication of the male haploid karyotype. By inference, these duplicated male pronuclei then proceeded to fertilize the female pronucleus.

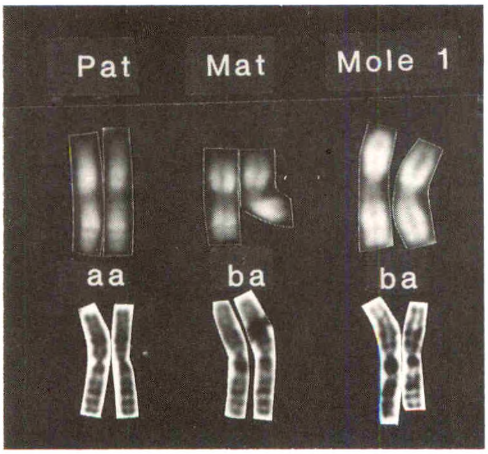

Fig. 4. Q-banded and Giemsa banded partial karyotypes showing the maternal contribution of chromosome 1 to the heterozygous cells. C-banding also confirmed this result but is not shown here.

Other cases which could be interpreted in a similar way to the present report are those of 'twin' moles. Several cases have been reported in the literature where either a completely normal pregnancy is found in conjunction with a mole 'twin' (Fisher *et al.* 1982; Yee *et al.* 1982) or some discrete part of the placenta is molar, in an otherwise normal pregnancy. In the light of the present evidence, those pregnancies may well have commenced as single eggs which underwent dispermic fertilization. Such cases would only differ from this case in the pattern of segregation of the two cell lines during the ensuing cleavage divisions. Explanation of the method by which a binuclear egg would eventually cleave to produce two mononuclear cell lines is an interesting problem in itself. Presumably the fate of the two nuclei is related to their positions relative to the first cleavage plane.

The critical event in the formation of the homozygous complete mole would seem to be sperm duplication. Furthermore, the strong association of sperm duplication with maternal ageing suggests that some parameter, which affects the sperm after fertilization, is altered in these eggs. Since the maternal (and not paternal) age is critical, this parameter is likely to be cytoplasmic and could well be cytoskeletal. Indirect evidence in man (Ford & Russell 1985) and direct observations in the eggs of old mice (Eichenlaub-Ritter *et al.* 1985) suggests that the microtubules of the spindle apparatus become dysfunctional with increasing maternal age.

Instability or reduced capacity of cytoplasmic microtubules may affect the behaviour of sperm after fertilization since at least two aspects of mammalian fertilization involve microtubular function. First, migration of the two pronuclei to the central region of the egg is under the control of cytoskeletal elements and can be prevented by microtubule inhibitors. Second, mitotic spindles are organized by maternal peri-centriolar material (PCM). These PCMs are readily dis-

Table 2. Polymorphic marker analysis

	Chromosome heteromorphisms*					
	3	13	14	15	21	22
Paternal	a b	a b	a b	a b	a b	a b
Maternal	a b	c d	c c	c b	c d	c c
Heterozygous molar cells	a b	a c	c b	c b	a d	b c
Homozygous molar cells	a a	a a	a a	b b	b b	b b

* a, b, c and d are symbols and do not represent specific heteromorphisms.

persed through the cytoplasm by treatment with microtubule inhibitors and, after removal of inhibitor, can induce multiple spindle poles (Howlett *et al.* 1985). Further, the male and female pronuclei undergo DNA replication independently. Thus if either migration or fusion of the pronuclei is delayed or fails, the probability of duplication of the unfused pronucleus is increased. This duplication might apply to male or female pronuclei or could be limited to the male.

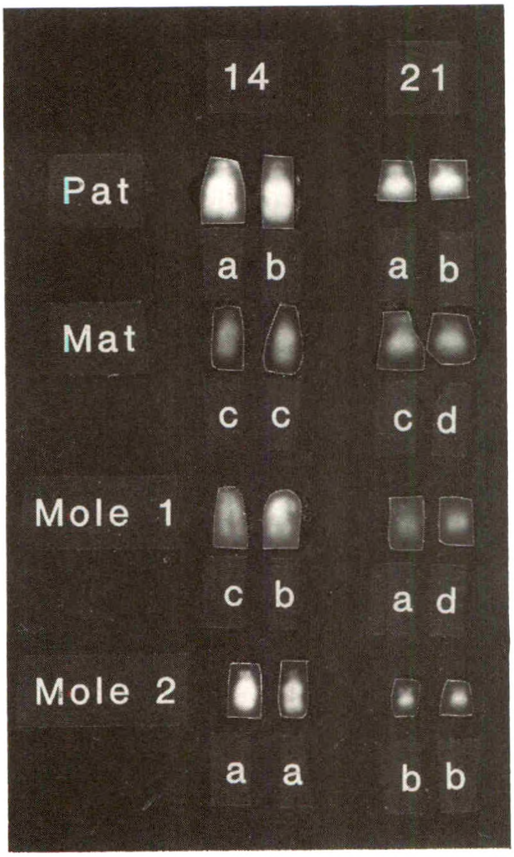

Fig. 5. The segregation of the informative chromosomes 14 and 21 is shown here. The symbols a, b, c and d are used to distinguish the chromosomes. The heterozygous cell line is depicted 'Mole 1' and the homozygous cell line, 'Mole 2'.

Dispermic fertilization is intrinsically liable to produce variable outcomes because to achieve triploidy the two male pronuclei must reach the female pronucleus simultaneously. Failure to do so would presumably exclude one pronucleus from fertilization, providing it with an enhanced opportunity for duplication.

This case provides evidence for the generation of a mosaic diploid mole by dispermic fertilization. The presence of a paternally-derived translocation has allowed us to detect mosaicism even though all cells had a 46,XX karyotype. The analysis has shown that two cell populations exist; one derived by normal fertilization with a female pronucleus and one by duplication of a male pronucleus. We have suggested that duplication of a male pronucleus could readily occur in an egg with reduced microtubule stability and such reduced stability might often be expected in the cells of older women. Where dispermy is involved in such fertilization, the result is possibly less predictable than for monospermy. Indeed, the final outcome would presumably depend on the position of the initial cleavage planes, as well as the relative viability and differential growth advantages of the various nuclei. Nevertheless, this case strongly suggests that male pronucleus duplication can occur in the presence of a competent egg nucleus.

The presence of a translocation has provided a rare opportunity to investigate thoroughly the cytogenetic origins of a complete mole. As far as we are aware, this is the first report of mosaicism in a 46,XX 'complete' mole. There is no reason to believe that the translocation itself should in any way affect the development of the mole. It is therefore surprising that the results obtained here are not consistent with the large body of data concerning the apparent non-mosaicism of complete moles. This anomaly leads us to suggest that the mosaicism described here is less rare than the literature implies. Perhaps there is 'hidden' mosaicism in some other moles which to date has defied conventional methods of detection. It seems plausible that cytogenetic analysis alone might often fail to detect mosaicism as long as one cell line was much rarer than the other. Perhaps more difficult to explain is the evidence from biochemical markers (e.g. Lawler *et al.* 1979). The sensitivity of the assays employed is clearly critical to the detection of mosaicisms and we would urge that this be considered in future studies of molar tissues.

This case raises questions about the possible results of dispermic fertilization. These are discussed in the light of information from other studies of molar and triploid pregnancies.

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Carcinoma of the gall bladder metastatic to the cervix. Case report

P. A. HALL, N. R. LEMOINE, J. F. RYAN

Case report

A 49-year-old white European woman presented in March 1980 with a short history of severe right hypochondrial pain and no significant past medical history. Acute cholecystitis was diagnosed and initially managed conservatively; she underwent an elective cholecystectomy some 6 weeks later. No unusual findings were noted at operation nor were any stones found in the gall bladder. Histological examination revealed signet ring adenocarcinoma arising from the gall bladder epithelium which showed dysplastic features (Fig. 1). Two months later she presented again with vaginal bleeding and was found to have ascites and a mass in the right iliac fossa. Vaginal examination revealed an eroded cervix and a cervical smear was taken. The cellular smear consisted of large pools of erythrocytes and polymorphs together with clumps of irregular malignant cells with eccentric hyperchromatic nuclei distorted by the presence of large mucin filled vacuoles (Fig. 2). These changes were regarded as adenocarcinoma.

At laparotomy numerous pale omental nodules were found in addition to an enlarged right ovary. No other abnormalities were found and in particular the liver and stomach were normal. Total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy were performed. Sections from the uterine cervix showed small nodules and cords of tumour cells similar to those seen in the gall bladder, surrounding endocervical glands and ulcerating the surface (Fig. 3). Similar tumour was present in the ovary but tumour was not present in the omental nodules which only showed fibrosis. The uterus and fallopian tubes were normal.

Postoperatively, despite chemotherapy she developed extensive lymphadenopathy in the neck, axillae and the groin. Over the ensuing 5 months she progressively lost weight, became increasingly jaundiced and her lymphadenopathy became more severe despite radiotherapy and chemotherapy. She died in November of that year. Permission for autopsy was withheld.

Discussion

Carcinoma of the gall bladder is an uncommon but serious disease usually affecting women past middle age. Most tumours are adenocarcinomas of intestinal type with variable amount of mucin secretion. Signet ring elements may be seen and can represent the bulk of the tumour (Gibson & Sobin 1978). The tumour in this patient was seen to arise from the surrounding gall bladder epithelium which showed markedly atypical features. This together with the operative findings of a normal stomach indicate that this was a primary adenocarcinoma of the gall bladder.

At the time of the first operation there was no clinical evidence of spread. The initial manifestation of dissemination of the tumour was vaginal bleeding and cervical cytology suggested that this was due to adenocarcinoma. The possibility of a secondary deposit was entertained and was confirmed by examination of the hysterectomy specimen. The clinical course following manifestation of metastasis of distant organs was of inexorable and rapid decline such as is typical of carcinoma of the gall bladder.

Only a single case of carcinoma of the gall bladder with cervical metastasis has been previously reported and no cytological findings

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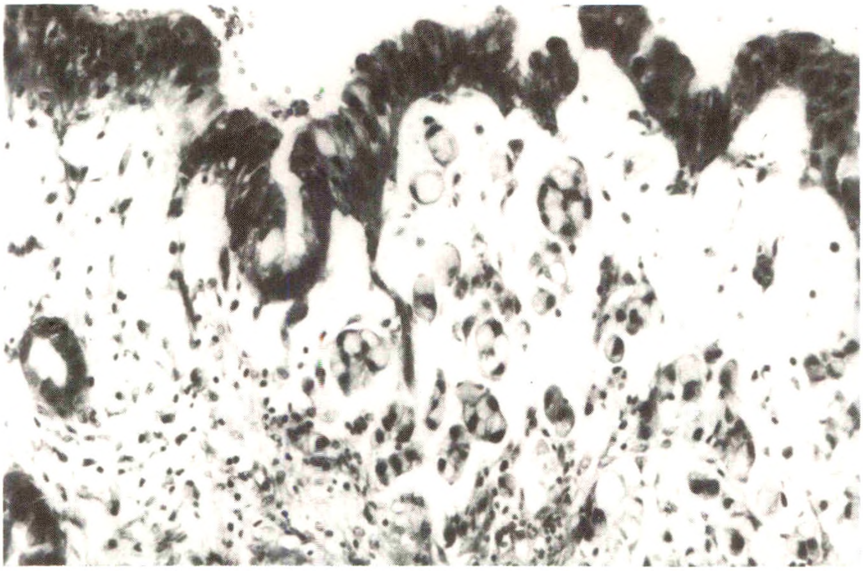

Fig. 1. Clumps of mucin-secreting adenocarcinoma including signet ring cells. The overlying epithelium shows marked atypia and nuclear hyperchromatism. Haematoxylin and eosin × 200.

were described (Fox & Sen 1967). Cervical biopsy revealed a secondary deposit of signet ring adenocarcinoma and a primary site in the gastrointestinal tract was suggested. Carcinoma of the gall bladder was found by autopsy. The authors described the secondary tumour as a 'Krukenberg' tumour because of its microscopic appearances regardless of its site. We feel that this term should be reserved for bilateral secondary deposits of signet ring adenocarcinoma in the ovary and not be used in the liberal manner advocated by Fox & Sen (1967).

The cytological features of secondary adenocarcinoma in the cervix have been described by Koss (1979) who emphasized that signet ring cells may be found in primary endocervical tumours as well as metastatic deposits from breast and large bowel, but who made no men-

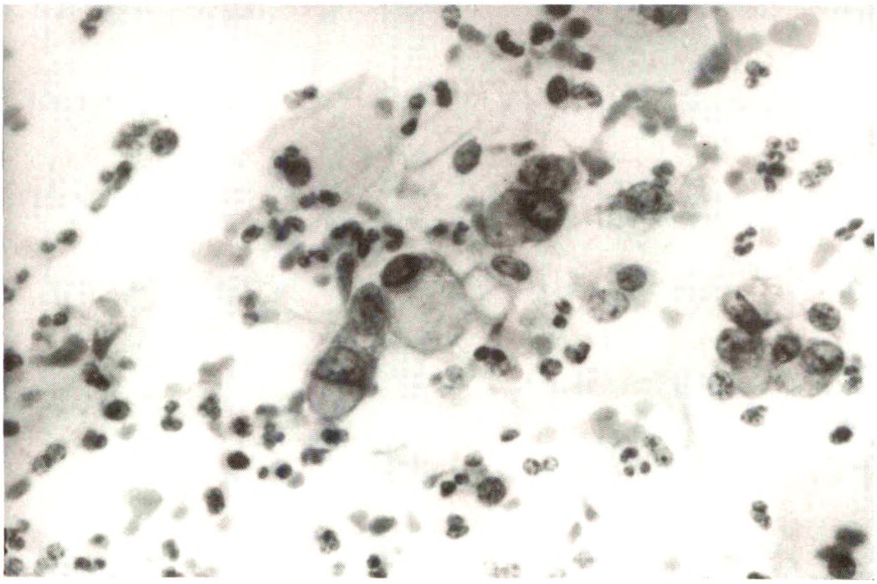

Fig. 2. Red cells and polymorphs together with pleomorphic mucin containing adenocarcinoma cells. Papanicolaou × 320.

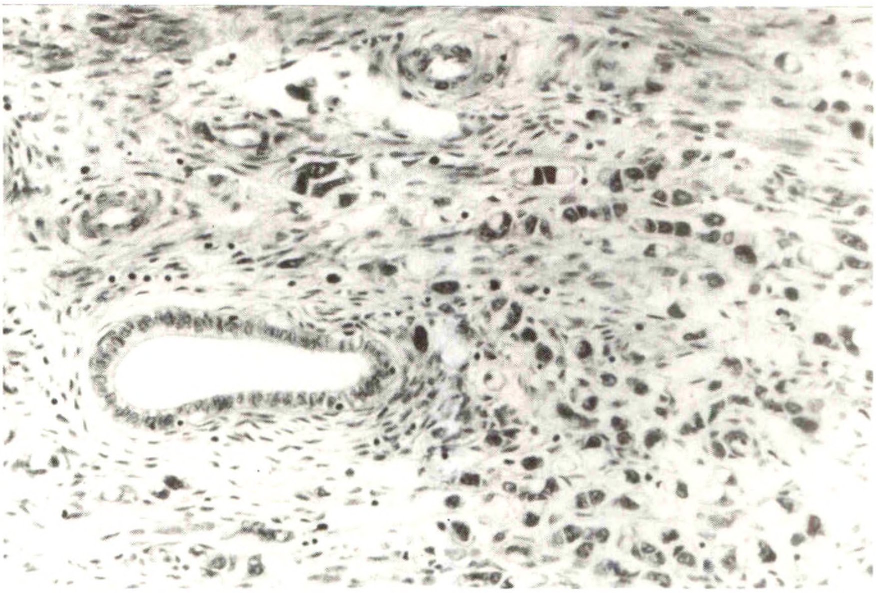

Fig. 3. The stroma surrounding a normal endocervical gland is infiltrated by cords and clumps of mucin-secreting adenocarcinoma with occasional signet ring forms. Haematoxylin and eosin × 200.

tion of gastric carcinoma as a possible primary site. Kashimura *et al.* (1983) and Zhang *et al.* (1983) stressed the presence of signet ring cells as a strong indication of a gastric primary origin, particularly in oriental populations. Other features said to suggest a metastatic lesion include large cellular area, larger nuclear area, more discrete vacuoles, increased nuclear membrane thickening and more coarsely granular chromatin pattern than in primary endocervical tumour (Kashimura *et al.* 1983) but these views are not universally held.

Metastases may arrive in the cervix by the blood stream or by retrograde lymphatic spread from blocked pelvic lymphatic channels. Direct spread from a secondary deposit in the ovary or pelvic peritoneum is a further alternative but can be excluded in this case on the basis of the laparotomy and macroscopical appearances. It may be that it is the poor vascularity of the cervix and its high content of dense fibrous tissue that explains the relative rarity of metastasis to the cervix.

Cases of epithelial tumours metastatic to the cervix have been described in the literature of which 76 arose in the gastrointestinal tract; 42 of these were gastric in origin; other common primary sites included breast, ovary and lung. In some cases, secondary deposits were incidental findings at the time of autopsy or in hysterectomy specimens, but in the majority of cases, cervical metastasis led to significant gynaecological symptoms. Occasionally, as in the case described by Fox & Sen (1967), symptoms due to the secondary deposit preceded the presentation of the primary tumour (Lemoine & Hall 1986). This case illustrates the most common mode of presentation of cervical metastasis with vaginal bleeding due to an ulcerated secondary deposit. We would emphasize that in any patient with a known malignancy and who presents with vaginal bleeding a cervical smear should be performed and the cytological appearances be interpreted in light of the full clinical picture.

Acknowledgments

We would like to thank Dr T. A. Lister, Mr R. A. Harlow and Dr H. Caplan for permission to report this case and Dr A. G. Stansfeld for reviewing the histology.

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SHORT COMMUNICATIONS

Maternal serum α-fetoprotein, birthweight and perinatal death in twin pregnancy

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Perinatal mortality rates for singleton pregnancies are now very low in developed countries but the rates for twin pregnancies remain high (Patel *et al.* 1984). Controversy still surrounds the value of long-term in-patient antenatal care in the prevention of perinatal death in twin pregnancy (Saunders *et al.* 1985). Since preterm birth and growth retardation are the main causes of perinatal death in twin pregnancies any biochemical marker of these complications would be valuable in antenatal management and the prevention of perinatal deaths.

Elevated levels of maternal serum α-fetoprotein (AFP) in second-trimester singleton pregnancies in the absence of neural tube defects, have been associated with an increased frequency of low-birthweight infants and increased perinatal loss (Brock *et al.* 1977, 1979; Wald *et al.* 1977; Purdie *et al.* 1983). A similar association has been suggested for twin pregnancies in other studies (Wald *et al.* 1978; Ghosh *et al.* 1982; Redford & Whitfield 1985), but not all the women had ultrasound scans in early pregnancy for gestational dating. The present study reviewed twin pregnancies delivered in Tayside Region during a 5-year period from 1st January 1980 to 31st December 1984 inclusive to investigate the relation between maternal serum AFP and birthweight and preventable perinatal loss in twin pregnancy.

Subjects and methods

Information on all multiple pregnancies of more than 20 weeks gestation in Tayside Region is held on a multiple pregnancy index file. One set of triplets was excluded from the study and pregnancies of less than 25 weeks gestation were excluded from the analysis.

Between 1st January 1980 and 31st December 1984 there were 246 twin pregnancies of ⩾ 25 weeks gestation delivered in Tayside Region. Adequate notes were available for 209 (85%) of these and 166 of the women had both a serum AFP and an ultrasound scan for gestational dating between 14 and 20 weeks gestation. Only one pregnancy was discordant for neural tube defect (one twin was anencephalic).

The maternal serum AFP was expressed as multiples of the median (MoM) AFP for the relevant gestation in singleton pregnancies not complicated by neural tube defect (Ninewells data, unpublished). Birthweight was recorded, and for infants born ⩾ 32 weeks gestation the birthweight centile was determined using the nomograms of Altman and Coles (1980). Fetal loss was measured at first week, first month and first year deaths. Spearman's rank correlation coefficient was used to assess the statistical relation between maternal serum AFP levels in early pregnancy and subsequent infant birthweight and gestation.

Results

Table 1 details the mean birthweight and gestational age at delivery according to the maternal serum AFP level. There was a tendancy for high AFP levels in early pregnancy to be associated with a lower birthweight ($r = -0{\cdot}12$) and earlier gestation at delivery ($r = -0{\cdot}16$) but this was not statistically significant ($P > 0{\cdot}05$).

Table 2 shows the distribution by birthweight centiles of twin pregnancies progressing beyond 32 weeks in relation to serum AFP. There was no significant increase in small-for-dates infants with increasing serum AFP levels.

The perinatal mortality for all twins born in Tayside during the 5 years studied was 14·3/1000. The infant mortality was 26·5/1000. The perinatal mortality in the 166 pregnancies that had an ultrasound scan for gestational dating and also maternal serum AFP estimation was 12·1/1000, with an infant mortality of 21·1/1000.

Table 1. Birthweight and gestational age in relation to maternal serum α-fetoprotein (AFP) in twin pregnancies

Serum AFP (MoM)	Number of pregnancies	Birthweight (g) Twin I	Birthweight (g) Twin II	Birthweight (g) Twin I + Twin II	Gestation at delivery (weeks)
<1	4	2·51 (0·4)	2·64 (0·2)	5·15 (0·49)	38·0 (1·6)
1–1 9	63	2·48 (0·48)	2·48 (0·46)	4·96 (0·87)	36·8 (2·3)
2–2·9	57	2·49 (0·54)	2·56 (0·48)	5·05 (0·97)	36·7 (2·4)
3–3·9	28	2·45 (0·59)	2·39 (0·57)	4·84 (1·14)	36·2 (2·7)
≥4	14	2·36 (0·47)	2·31 (0·52)	4·67 (0·91)	36·0 (2·7)

MoM, Multiples of the singleton median
Results are means (SD).

The perinatal, first month and first year deaths are shown in Table 3. There were no deaths in association with serum AFP levels in early pregnancy of > 4 MoM for singleton pregnancies except one twin which was anencephalic (AFP=7·8 MoM).

Discussion

An inverse relation between elevated maternal serum AFP and birthweight has been demonstrated for singleton pregnancies (Brock *et al.* 1977; Wald *et al.* 1977; Purdie *et al.* 1983). Wald *et al.* 1978) described a similar association for twin pregnancies were unable to determine whether the low birthweight was due to an increased frequency of preterm births or small-for-dates infants because of the infrequent use of ultrasound scans to confirm gestational age. One of the most common causes of an apparently high serum AFP level is incorrect dates and without ultrasound scanning it is difficult to interpret maternal serum AFP levels. An apparent elevation of serum AFP due to underestimated gestation will necessarily lead to premature delivery. In our study, where gestation was confirmed by an ultrasound scan in all cases, no association was found between a high AFP in early pregnancy and subsequent preterm delivery.

In the present study birthweight centile for gestational age was calculated to determine whether there were more small-for-dates infants associated with elevated AFP levels in early pregnancy, but here again no significant difference was found.

Ghosh *et al.* (1982) reported a high fetal loss in association with elevated AFP levels in twin pregnancies. Of 17 twin pregnancies with maternal serum AFP levels of > 5 MoM for singleton pregnancies at between 15 and 20 weeks gestation only seven resulted in normal liveborn twin pairs. However, their study included as fetal losses seven spontaneous abortions, and two fetus papyraceous; there was only one stillbirth. We have excluded pregnancies ending at < 25 weeks gestation and fetus papyraceous, regard-

Table 2. Distribution by birthweight centile in relation to maternal serum α-fetoprotein (AFP) in twin pregnancies

Maternal serum AFP (MoM)	Number of pregnancies	Birthweight centile* <3 n (%)	Birthweight centile* 3–10 n (%)	Birthweight centile* 11–50 n (%)	Birthweight centile* >50 n (%)
<1	4	2 (25)	3 (37·5)	3 (37·5)	—
1–1·9	61	13 (10·6)	34 (27·9)	67 (54·9)	8 (6·6)
2–2·9	53	13 (12·3)	17 (16·0)	60 (56·6)	16 (15·1)
3–3·9	25	6 (12 0)	14 (28·0)	20 (40·0)	10 (20·0)
≥4	13	3 (11·5)	5 (19·2)	16 (61·5)	2 (7·7)

*Calculated from nomograms for singleton pregnancies (Altman & Coles 1980).
MoM, Multiple of the singleton median
χ^2 test for trend = 1·74; P=0·19 (not significant)

Table 3. Perinatal, first month and first year death in relation to maternal serum α-fetoprotein (AFP) in twin pregnancies

Maternal serum AFP (MoM)	Number of pregnancies	Stillbirths	Neonatal deaths <7 days	Neonatal deaths 7–<28 days	Postnatal deaths 28 days–<1 year
<1	4				
1–1·9	63			1	1
2–2·9	57	1	1	1	2
3–3·9	28		1		
4–4·9	10				
≥5	4	1			

MoM, Multiples of the singleton median.

ing these as obstetric events over which obstetricians have little influence. Fetus papyraceous in particular tends to be poorly documented and with increasing use of ultrasound in early pregnancy, it is apparent that one sac of a twin pregnancy often disappears although no obvious fetus papyraceous is seen on placental examination at delivery (Varma 1979). Apart from one anencephalic fetus there were no perinatal or first year deaths in twin pregnancies where the maternal serum AFP level was > 4 MoM.

Although a high maternal serum AFP may alert the obstetrician to the presence of a multiple pregnancy it does not appear to be of value in discriminating those twins at increased risk of preterm delivery, being small-for-dates or dying in the first year of life.

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting in May 1986 at the Royal College of Obstetricians and Gynaecologists

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Studies of the effect of a luteinizing hormone releasing hormone (LHRH) agonist (Buserelin) in patients with uterine leiomyomata by W. Matta, R. W. Shaw & M. Nye. Department of Obstetrics and Gynaecology, Royal Free Hospital, Pond Street, London NW3 2QG

It has long been recognized that uterine leiomyomas are oestrogen-dependent. The finding that repeated administration of LHRH agonists cause reversible inhibition of the hypothalamic-pituitary-ovarian axis and a state of hypo-oestrogenism suggested a possible new approach in the treatment of uterine leiomyomas. The LHRH agonist D-Ser (TBu^6)-des-Gly-NH_2^{10}—LHRH ethylamide (Buserelin Hoechst) was given at doses of 300 or 400 µg three times daily intranasally to groups of 10 patients with a control group of four patients receiving no treatment. Treatment was continued for 6 months, with monthly reviews and ultrasound and clinical assessment of uterine size and follow-up for 6 months. Low circulating oestradiol values were induced in all patients, with a mean value of 110 pmol/l and 81 pmol/l after 3 months on 300 µg and 400 µg respectively. Significant but variable reduction in uterine size was achieved with mean values of 42% and 46% of control values at 6 months in the 300 and 400 µg groups respectively. No significant changes were seen in the control groups. A gradual increase in size was observed in many patients when treatment was stopped. We conclude that this conservative approach may be of value in certain patients with uterine leiomyomata.

Suppression of pituitary gonadotrophin release with a luteinizing hormone releasing hormone (LHRH) analogue before superovulation for in-vitro fertilization (IVF) by B. Bentick, G. Burford, A. G. Bernard & R. W. Shaw. Academic Department of Obstetrics and Gynaecology, Royal Free Hospital, Pond Street, London NW3 2QG

Twenty-two patients on an IVF programme were given HOE 766 (Buserelin, Hoechst), an LHRH analogue, by intranasal spray 100 µg every 4 h from the mid-luteal phase for 15 days, when either pure FSH (Metrodin, Serono) or human menopausal gonadotrophin (hMG) (Pergonal, Serono) was added at a dose of two ampoules daily intramuscularly. In nine of the 11 patients in the Metrodin group, laparoscopy retrieved 65 oocytes, 44 (68%) of which fertilized, leading to eight transfers of 27 embryos (3·38/transfer); four viable pregnancies resulted (two twins). In eight of the 11 patients in the hMG group, laparoscopy retrieved 30 oocytes, 24 (80%) of which fertilized, leading to six transfers of 16 embryos (2·67/transfer). One pregnancy resulted and terminated in a missed abortion at 8 weeks gestation. Both in the hMG- and Metrodin-treated groups, after an initial stimulated release, suppression of LH and FSH levels was achieved by day 11 of Buserelin. In the hMG-treated group serum oestradiol fell from a baseline of 822 pmol/l (SEM 185) to 127 pmol/l (SEM 37·93) on day 15 of Buserelin, rising to 1643 pmol/l (SEM 330) on day 10 of hMG. On average 13·13 (SEM 1·48) days stimulation with 29·75 (SEM 4·87) ampoules of hMG were required to initiate follicular growth. In the Metrodin group serum oestradiol fell from a baseline of 1424 pmol/l (SEM 238) to 247 pmol/l (SEM 88) on day 15 of Buserelin, rising to 5255 pmol/l (SEM 2692) on day 10 of FSH. On average 10·67 (SEM 0·44) days stimulation with 21·33 (SEM 0·88) ampoules of FSH were required. Peak oestradiol per viable follicle (≥15 mm diameter) was similar for each group; 1689 pmol/l (SEM 558) in the hMG group and 1483 pmol/l (SEM 238) in the FSH group. This treatment is effective for superovulation for IVF and overcomes some of the common problems, though the duration of stimulation is prolonged compared with standard superovulation protocols.

Bacterial colonization and preterm labour: alterations in non-specific host defence? by K. S. Toth, A. D. Noble & A. T. Letchworth. Royal Hampshire County Hospital, Winchester, Hants SO22 5DG

The association between bacterial colonization of the vagina and preterm labour was studied prospectively. Patients were divided into three groups: a study group of 36 women who went into labour and were delivered before 37 weeks gestation, a control group of 20 women who were admitted in preterm labour but were delivered after 37 weeks and a second control group of 18 normal women who were delivered spontaneously at term. No patient with potential causes of preterm labour other than infection was included. The bacterial flora of the vagina and cervix was examined together with the histology of the placenta, membranes and umbilical cord. Maternal serum iron, transferrin, ferritin and C-reative protein were measured to assess the non-specific host defence system in preterm labour. There were no significant bacteriological differences between the groups. Bacterial colonization in patients with premature rupture of the membranes was similar to that of patients with intact membranes. Histological chorioamnionitis with clinical evidence of infection was found in 14% of the study group, and without clinical evidence of infection in 10% of all groups. Haemoglobin, transferrin and the proportion of patients given iron supplements were similar in all groups but patients in the study group had lower serum iron, higher serum ferritin and C-reactive protein especially those with clinically evident infection. The non-specific host defence reaction may explain why infection with the same organism is associated with preterm labour in some patients but not in others.

Seminal analysis and clinical sperm function tests: definition of normal values using in-vitro fertilization (IVF) by P. G. Wardle, E. A. McLaughlin, J. A. C. Williams, J. D. Mitchell, P. A. Foster, E. Corrigan, B. D. Ray, A. McDermot,* & M. G. R. Hull. University Department of Obstetrics and Gynaecology, Bristol Maternity Hospital, Bristol BS2 8EG and *Regional Cytogenetics Centre, Southmead Hospital Bristol BS10 5ND

We studied 118 infertile couples undergoing IVF at the time of diagnostic laparoscopy, they had been fully investigated previously. The study focused on sperm function by excluding couples with functional female disorders, and by restricting analysis to the fertilization of morphologically mature oocytes. Using fertilization *in vitro* as an end-point the aims of the study were to determine critical seminal values for normal fertility, and to compare seminal analysis with functional tests of sperm-mucus penetration. The results showed that standard seminal analysis alone was a poor prognostic indicator of in-vitro fertilizing capacity of spermatozoa except when the three elements—density, progressing motility and normal morphology—*all* fell below the individually derived critical levels (40×10^6/ml, 40% and 40% respectively). The fertilization rate per oocyte was 67% when all elements of the seminal analysis were above critical levels and 54%, 40% and 8% when one, two or all three respectively fell below critical levels. In-vitro sperm-mucus invasion testing (K-M test) was a better prognostic indicator of sperm fertility than standard seminal analysis. The fertilization rate per oocyte was 61% when the K-M test was positive and only 20% when the result was negative. The post-coital test (PCT) was the best prognostic indicator of sperm fertility. The fertilization rate per oocyte was 72% when the PCT was positive and only 16% when the result was negative. The superiority of the PCT over the K-M test in its predictive value for fertility is likely to be due to it being a test of prolonged sperm survival as well as penetration capacity.

The relative diagnostic value of seminal analysis, sperm antibody assays and a modified in-vitro sperm-mucus invasion test (SMIT) in infertile couples with negative post-coital tests, and a controlled trial of AIH treatment by C. M. A. Glazener, N. J. Kelly, C. Coulson, P. A. Lambert, E. M. Watt, R. A. Hinton & M. G. R. Hull. University of Bristol Department of Obstetrics and Gynaecology, Bristol Maternity Hospital, Bristol BS2 8EG

Failure of sperm-mucus penetration was identified as a cause of infertility in 94 couples after excluding overt coital dysfunction. The reason for the failure, as strictly defined by repeated negative post-coital tests (PCT), was determined by (1) standard seminal analysis (normal at least 4×10^6/ml motile normal spermatozoa); (2) in-vitro slide sperm-mucus invasion test (SMIT, modified K-M test); (3) MAR; (4) TAT on seminal plasma; (5) TAT on cervical mucus. The SMIT was found to correlate closely with seminal analysis (90% agreement, $P<0{\cdot}001$) and the antibody assays on semen (81% agreement, $P<0{\cdot}001$), and appeared to be more reliable when the other tests were discordant. We concluded that the SMIT is both an accurate and simple, and therefore the most useful, means of diagnostic categorization of couples with a negative PCT. There were too few TAT results on mucus to be diagnostic in that respect. We found that 38% of couples with negative PCT had poor seminal quality and 34% had seminal sperm antibodies. Sperm survival despite invasion of mucus was impaired in 11% for uncertain reasons presumably including sperm antibodies in mucus and functional defects inherent in the mucus or spermatozoa. The remaining 17% had normal invasion and survival indicating undisclosed coital failure in some cases. In a subset of 46 couples in whom female causes of infertility were excluded, a controlled trial of artificial insemination with husband's semen (high AIH) in 223 cycles versus natural intercourse in 252 cycles revealed no benefit (two and three pregnancies in the respective groups) even when seminal quality or the presence of seminal sperm antibodies was taken into account.

Endometriosis and infertility: a true causal association? by P. A. Foster, A. Foulkes & M. G. R. Hull. University of Bristol Department of Obstetrics & Gynaecology Bristol Maternity Hospital, Bristol BS2 8EG

The true association between endometriosis without major structural damage, and infertility remains elusive. We studied the question by comparing infertile women with and without endometriosis in two ways: by retrospective analysis of associated functional disorders, through which endometriosis may be the cause of infertility; and by prospective analysis of conception rates without treatment. We found no specific functional disorder to account for infertility, but fertility was significantly reduced, particularly in women whose endometriosis involved the ovaries. We speculate that endometriosis causes infertility by a direct effect on follicular function. We compared at laparoscopy 76 women with endometriosis, 60 with normal pelvic findings, and 58 with inflammatory tubal damage. There were no significant differences in the rates of oligo-amenorrhoea (0, 6% and 2% respectively), luteal deficiency (15%, 8%, 16%) or oligospermia (27%, 29%, 19%), but there was a reduction in sperm-mucus penetration failure in the tubal group (24%, 24%, 7%, $P<0{\cdot}01$). The cumulative conception rate at 2 years was significantly reduced in the endometriosis group (21%, SE 10·5%, $P<0{\cdot}01$) compared with the normal pelvis group (52%, SE 10%). The rate was also reduced in the 47 women with minimal endometriosis (28%, SE 12·5%, $P<0{\cdot}01$), and was markedly reduced in those with ovarian involvement (32) (9%, SE 11·5%, $P<0{\cdot}01$).

Menopausal flushes and sympathetic activity by Margaret C. P. Rees, D. H. Barlow, C. J. Glynn & A. C. Turnbull. Nuffield Department of Obstetrics & Gynaecology and Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford OX3 9DU

Hot flushes are a common distressing menopausal problem associated with an acute increase in skin temperature, blood flow and cutaneous vasodilation. Skin blood flow is controlled by tonic sympathetic adrenergic vasoconstrictor activity. This study was undertaken to explore cutaneous sympathetic nervous system control using the vasoconstrictor ice response of hand blood flow in 10 flushing menopausal women, six non-flushing menopausal women, 22 premenopausal women and eight men. Nine of the 10 women experiencing hot flushes lacked the vasoconstrictor ice response present in all the other groups examined, suggesting an abnormality of sympathetic nervous system control of skin blood flow. The abnormality was independent of a flush episode since only one woman had a flush during testing. The data therefore indicate a persistent impairment of sympathetic control of skin blood flow outwith the individual episodes of neuroendocrine discharge which result in flushes.

Fetal steroid binding glycoprotein by Maureen E. Dalton & Carl L. Ambrose. Department of Obstetrics and Gynaecology, St James's University Hospital, Leeds LS9 7FT

Fetal steroid binding glycoprotein (FiSBoG) is a recently described protein. By Scatchard analysis, it has the binding pattern of a single binding site. It binds dihydrotestosterone (DHT), testosterone and oestradiol with K^a of $6{\cdot}4 \times 10^8$, $3{\cdot}7 \times 10^8$, $1{\cdot}4 \times 10^8$ respectively. Its estimated molecular weight is 35 000 daltons by sucrose density ultracentrifugation. This high affinity binding protein is not sex hormone binding globulin (SHBG) as it does not bind androstenediol or androstenedione and it does bind on Cibracon blue F3GA Sepharose 6B, which SHBG does not. Human fetal steroid binding protein is an intracellular hepatic protein with an allosteric binding protein so it is different, although possibly closely related, protein. FiSBoG is not found in non-pregnant adults by present assay methods but purification of this glycoprotein for the raising of an antibody is in progress. The assay involves removing albumin by ammonium sulphate precipitation, incubating the reconstituted precipitate with 3H DHT and increasing amounts of cold DHT, passing the sample down a column of Cibacron blue F3GA Sepharose 6B and then washing the column, counting the radioactivity and using Scatchard analysis to quantify FiSBoG. In early pregnancy (before 20 weeks) FiSBoG was present in higher quanitites in fetal blood compared with maternal blood and was present in amniotic fluid. By late pregnancy this had changed—there being no FiSBoG detectable in amniotic fluid. In late pregnancy there was no sex difference in cord or maternal blood and no significant changes with gestation or birthweight. Higher values were found in maternal plasma in twin pregnancies, after antepartum haemorrhage and stillbirth but not in small-for-dates pregnancies.

Doppler assessed uterine blood flow in the first trimester of pregnancy. I. Stabile, A. Sacks, S. Campbell & J. G. Grudzinskas. The London and King's College Hospitals, London.

Thirty-three women with uncomplicated pregnancies, and 20 women with threatened abortion at 6–16 weeks gestation were recruited for pulsed wave and continuous wave Doppler assessment of flow through the uterine arteries. The differences in measurements observed with either apparatus were always less than 5%. The resistance index (RI), and A/B values were measured in relation to gestational age and the occurrence of painless vaginal bleeding. A downward trend in resistance to flow was seen with advancing gestational age in the first trimester. This gradual decline in RI is consistent with earlier findings of the typical arcuate artery flow velocity waveforms in the second trimester, the time when trophoblastic erosion of the spiral arteries occurs. Our findings indicate that the downward trend in resistance to flow commences earlier in pregnancy. Maternal uterine blood flow in the first trimester does not appear to differ in women with threatened abortion who have a normal outcome, and we are expanding our data base to explore the possibility that a change in resistance index may be of prognostic value for subsequent complications.

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BOOK REVIEWS

Understanding Abortion by Mary Pipes. The Women's Press Handbook Series, London, 1986, 181 pages, £3.95

The author a freelance executive for a London public relations company, has written a manual of abortion which will be welcomed by those seeking to increase their skill in abortion counselling. Practical aspects are explained clearly, as are also the birth control methods for preventing a further unwanted pregnancy. The text is interspersed with comments written or spoken by some 30 British and Irish women who have undergone abortion. The feelings they express evoke sadness and concern for the practical and emotional conflicts they suffered. In many cases they did not have appropriate help to use the experience to gain self-understanding and live more constructively afterwards.

The text is written in the first person, implying that the author identifies strongly with these women. She states that her aim is to inform about the emotional, medical and legal aspects of abortion, and also 'to make it easier for women confidently to claim the right to control their bodies in the widest sense, and to view abortion as a positive affirmation of that right.' They can then 'refute the arguments of those who label them as selfish and feckless'.

Behind this statement there is anger about medical staff who fail to value women in vulnerable situations, or to share the pain of loss. There are no quotes from the putative fathers, whose feelings are not treated with much consideration. The same applies to putative grandparents, and to the gynaecologists who have what they may see as the unhappy task of performing the operation.

The anger of some of these women seems to be a resentment against being female and feeling out of control of life events. There is acknowledgment that the real cause of the anger 'lies with some deeper emotion such as previous loss or rejection dating back to childhood,' and that counselling in depth may be the only way to discover the roots of such negative feelings.

The good description of feelings after an abortion, both immediate and distant, makes it clear that counselling is often needed to help a woman come to terms with the cause of unwanted pregnancy such as, for instance, the inadequate or inappropriate mothering that she received as an infant.

The declared intention of the book is 'to counteract Society's disapproval of abortion.' It might have been still more useful had it explored more fully ways of understanding and helping individual women who fail to control their fertility for covert reasons and, finding themselves pregnant, experience ambivalent feelings about being the mother of a child.

Robina Thexton

The Pharmacology of the Urinary Tract edited by Marco Caine. Springer-Verlag, Berlin, 1984, 167 pages with figures and tables, DM 98

Recognition of the importance of pharmacology of the urinary tract has come late in the day. It has been due in part to the relative immunity of bladder and urethra to drug action and the lack of interest displayed in this area by clinical pharmacologists and the pharmaceutical industry.

Professor Marco Caine is an internationally known urologist who has himself researched and written in this area: he is the editor of a team of equally well known urologists, having similar research and clinical experience in their subjects. He has contributed the first three chapters which are lucidly written and comprehensively reviews the relevant neurophysiology, neuropharmacology, neurotransmitters and classification of pertinant pharmacological agents. The remaining chapters deal with the treatment of functional disorders of the upper and lower urinary tracts, finally concluding with a more speculative chapter on the treatment of the several urological enigmata, some of which are certainly in the province of the gynaecologist.

My only criticism concerns the chapter on the neuropathic bladder, which I thought was unclear: 'neurogenic' and 'neuropathic' were undefined and randomly interchanged, the classification of neuropathy was diffuse and both examples of filling cystometry used fast rather than slow filling techniques. Tighter editing of the chapter would have avoided some repetition on therapy.

There are few available texts on this subject. This volume is well-referenced and clinically orientated and should appeal to all clinicians with an interest in treatment of disorders of lower urinary tract function. I would commend it especially as a bench book to any urodynamic unit.

Stuart L. Stanton

Obstetrics and the Newborn. An Illustrated Textbook. Second British Edition by Norman A. Beischer & Eric V. Mackay. Baillière Tindall, London, Philadelphia, 1986, 770 pages with figures and tables £14.95

'A week is a long time in politics'. Similarly it can be said that a decade is a long time in obstetric practice and in this time span many changes take place. It is not surprising, therefore, that the Second Edition of *Obstetric and the Newborn* in enlarged to 770 pages from 532 which was the length of the First Edition published 10 years ago. The increase in size arises from a careful balance between giving additional information to bring the reader up-to-date as exemplified in the chapter on 'Special investigative procedures' and the subtle changes in emphasis in obstetric practice associated with better patient education and what the authors describe as the 'family-centred approach'.

More coloured and black and white illustrations have been added which clarify the text admirably. The plates depicting unusual fetal anomalies are especially valuable.

Each chapter is preceded by an 'overview' of the subject about to be discussed which helps to focus the reader's attention. This feature proved popular in the authors' companion book *Illustrated Textbook of Gynaecology* and will be similarly appreciated in this book. It should prove particularly helpful to medical students and pupil midwives revising for examinations.

Since the book is aimed principally at medical and midwifery students, as well as primary care physicians, all aspects of normal and abnormal antenatal, perinatal and postnatal conditions are lucidly described and frequently illustrated. The chapters on neonatal care are closely related to the appropriate obstetric care which is as it should be in practice.

The book is beautifully produced and its dark blue cover with contrasting white and yellow lettering is eye-catching. It is modestly priced for its presentation and content. It can be recommended for both undergraduate and postgraduate students (medical or nursing) and all others engaged in clinical obstetric practice and many relatively mature 'students' could well make use of it to bring their lectures up-to-date.

John McVicar

Gynaecology Illustrated Fourth Edition edited by A. D. T. Govan, C. Hodge & F. Callander. Churchill Livingstone, Edinburgh, 1986, 490 pages with figures and tables, £11.50

This is the Fourth Edition of a well-known volume first produced in 1972. It presents to the student a simple account of gynaecology in which diagrams play a major part. The illustrations are well known and are well done in the format of black and white line drawings. There are no photographs and no colour but Robin Callander has managed to produce illustrations to help the understanding of many of the concepts as well as simple anatomy or structural surgery.

The illustrations for abdominal and bimanual examinations are excellent teaching material showing exactly what needs to be considered. Throughout, the illustrators have taken a sensible line in illuminating those areas they think they can, but the lack of colour is apparent in places, such as vulval dystrophy where the illustrators have tried to show the histology in black and white while we mostly see it on slides in colour. A different area is the consideration of urinary incontinence and here the illustrators have taken us through the symptoms, signs and investigation of the subject and then shown very neatly the methods of trying to cure it.

This book is recommended to all medical students (along with the companion volume on obstetrics) as an adjunct of learning. If they have this in their library with a standard textbook of gynaecology, they will be able to visualize what is happening in the subject far better than just looking at most standard textbooks for the figures are much clearer.

Geoffrey Chamberlain

Books received some of which may be reviewed at a later date

Clinics in Obstetrics and Gynaecology. Volume 13, No. 2. Prescribing Pregnancy edited by

Gordon Stirrat & Linda Beeley. W. B. Saunders Company, London, 1986, 161–420 pages with figures and tables, £13.50

Basic Sciences for Obstetrics and Gynaecology Second Edition by Tim Chard & Richard Lilford. Springer–Verlag, Berlin, Heidelberg, 1986, 195 pages with figures and tables, £15.00

Diethystilbestrol—New Perspectives by David Edelman. MTP Press Ltd., Lancaster, 1986, 180 pages with figures and tables, £39.95

MRCOG PART I Practice Exams by Paul Hilton, David Ireland & Keith Godfrey. Pastest Service, Hemel Hempstead, 1986, 176 pages, £8.50 paperback

The New Fertility. A Guide to Modern Medical Treatment for Childless Couples by Graham H. Barker. Adamson Books, London, 1986, 176 pages illustrated, paperback £5.95, hardback £9.95

Medical Problems in Pregnancy: Their Diagnosis and Management by John F. Mayberry, Andrew P. Bond & John S. Morris. Edward Arnold, London, 1986, 214 pages with figures and tables, £9.50

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG. Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript. The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution; major changes will be agreed with the author(s).

Presentation of manuscripts

Two copies of the manuscript and illustrations should be sent. Manuscripts should be typed double spaced on one side of the paper, with wide margins. The names of author(s) and their appointment(s) and addresses at the time of preparation of the manuscript should be given. Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss.

Reports of original work should usually be arranged in the conventional order of summary, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used, the third order heading runs on with text at a paragraph opening. Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables. The summary should contain a factual account of the methods and results in not more than 150 words, rather than a description of the subject of the paper and the opinions of the author(s).

Case reports and short communications do not require a summary or introduction. Short communications should not exceed 600 words and contain no more than one table or figure.

Tables and figures

Tables and figures should be separate from the text, with their positions indicated in the text margin. Both are numbered with arabic numerals. Colour illustrations are allowable only in special circumstances and the author will be expected to meet the cost of reproduction.

Figures should be marked on the back (light in pencil) with the name(s) of the author(s), the figure number, and the top indicated. Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast.

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc. Tables are not included in this classification and should not be submitted as photographs. Original X-ray films should not be sent—glossy prints must be submitted.

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column).

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself.

The identity of patients in illustrations should be concealed by masking the face or eyes, or written permission for publication from the patient or the parent or guardian must be supplied.

Units and abbreviations

Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg). If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors. Standard abbreviations, without punctuation, are used. *Units, Symbols and Abbreviations* (1977) published by the Royal Society of Medicine provides a useful guide. Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both summary and text, followed by the abbreviation in parenthesis.

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

Statistics

Authors should describe clearly the design of their investigation and the source of the data. All statistical methods should be specified so that it is clear which was used where. Papers omitting this information may be returned without review. The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else.

Some points of detail to note are:

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic.
(2) The use of confidence intervals is encouraged.
(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean ... was 14·2 (SD 3·2) mg' is preferred.
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
(5) Unusual methods of analysis should be described and/or referenced.

Authors are referred to the general statistical guidelines of Altman *et al* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286,** 1489–1493.

Human experiments

Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work. The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References

In the text, use the name of the author(s) followed by their date of publication; where there are two authors use the form Smith & Brown 1972; where there are more than two authors use Robinson *et al* 1979.

Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows.

Name(s) and initials of all author(s), year of publication (in brackets), title of the article, name of the journal (abbreviated according to *Index Medicus*), volume number, first and last page numbers. In the case of books the order is: Name(s) and initials of author(s), year of publication (in brackets), full title, edition, publisher and place of publisher, page numbers. Where appropriate, the chapter title and the names of the editors should be given.

References to 'personal communications' and 'unpublished work' may be quoted in the text but should not be included in the references. Examples of the style to be used are given below.

Trudinger, B. J., Lewis, P. J. & Petit, B. (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86,** 432–436.

Hytten, F. E. & Leitch, I. (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p. 26.

Proofs and offprints

Manuscripts should specify the name and address of the author to whom correspondence and page proofs should be sent. Only essential corrections can be accepted, more extensive alterations, which may delay publication, will be charged to the author. Fifty offprints of each paper are supplied free, but additional copies may be ordered on the printed card sent with the proofs.

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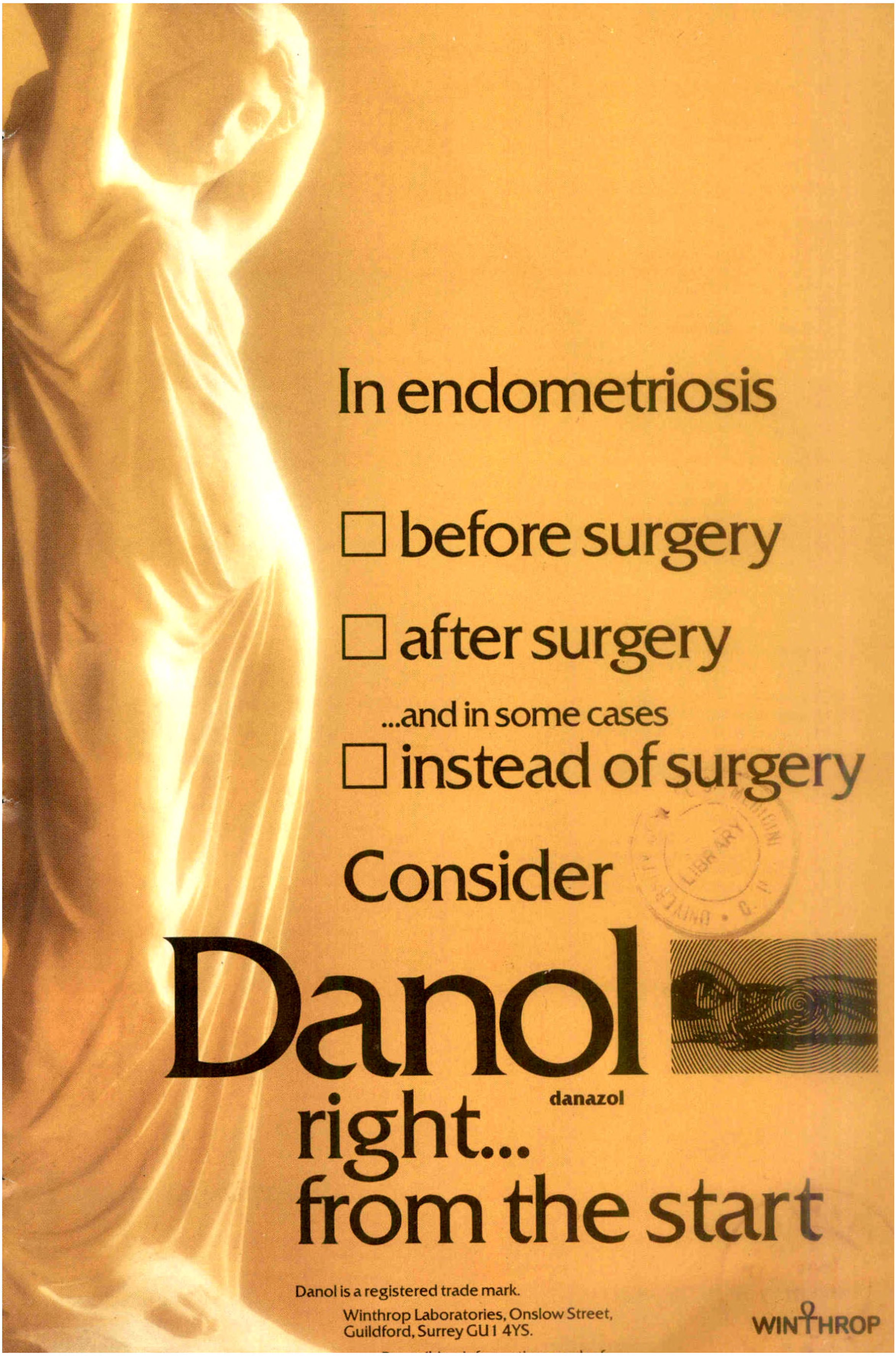

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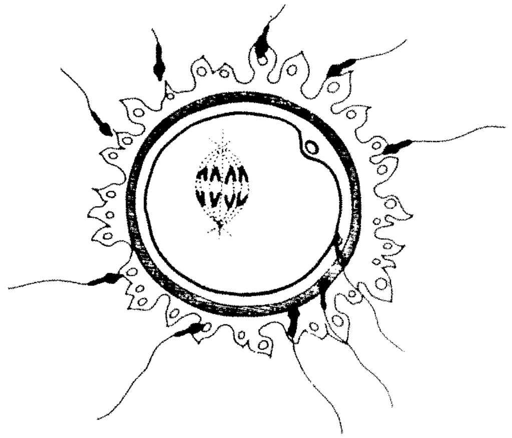

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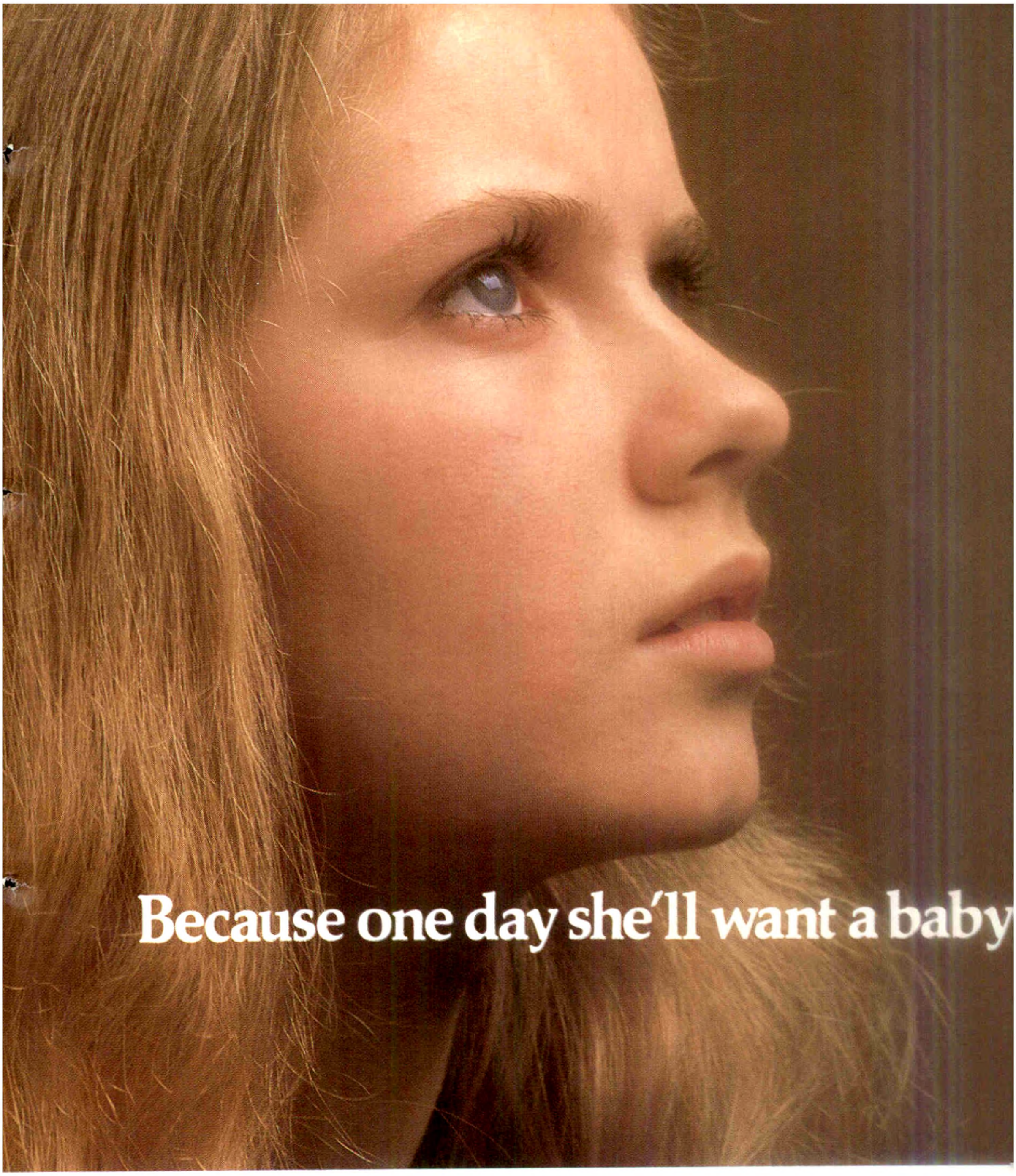
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›sage One pessary 3 hours before surgery. Allow pessary to warm to om temperature in unopened foil sachet before use. **Contra-dication** Hypersensitivity to prostaglandins. **Precautions** Use with ution in patients with obstructive airway disease, cardiovascular sufficiency, elevated intra-ocular pressure, cervicitis or vaginitis. ›ep patient under observation if surgery is postponed much beyond ›urs after insertion of pessary as abortion may occur. Follow up of ıtient essential to ensure termination has been completed as effect of meprost on foetus has not been established. Do not use Cervagem r induction of labour or cervical softening at term. **Side-Effects** ıginal bleeding, mild uterine pain. Nausea, vomiting, diarrhoea, ›adache, muscle weakness, dizziness, dyspnoea, chest pain, mild ›rexia. **Presentation** Pessary containing 1mg gemeprost in carton of unit dose foil sachets. **PL No.** 0012/0149. **Basic NHS Cost** (April ›86) £82.50 per box. **References:** 1. Harlap,S. *et al.*, *N.Eng.J.Med.*, ›79, **301,** 677. 2. Richardson,J.A. & Dixon,G., *Brit.Med.J.*, 1976, **1,** ›03. 3. Chen.J.K. & Elder,M.G., *Obstet.Gynecol.*, 1983, **62,** 339. . Christensen,N.J., Bygdeman,M. & Gréen,K., *Contraception*, 1983,

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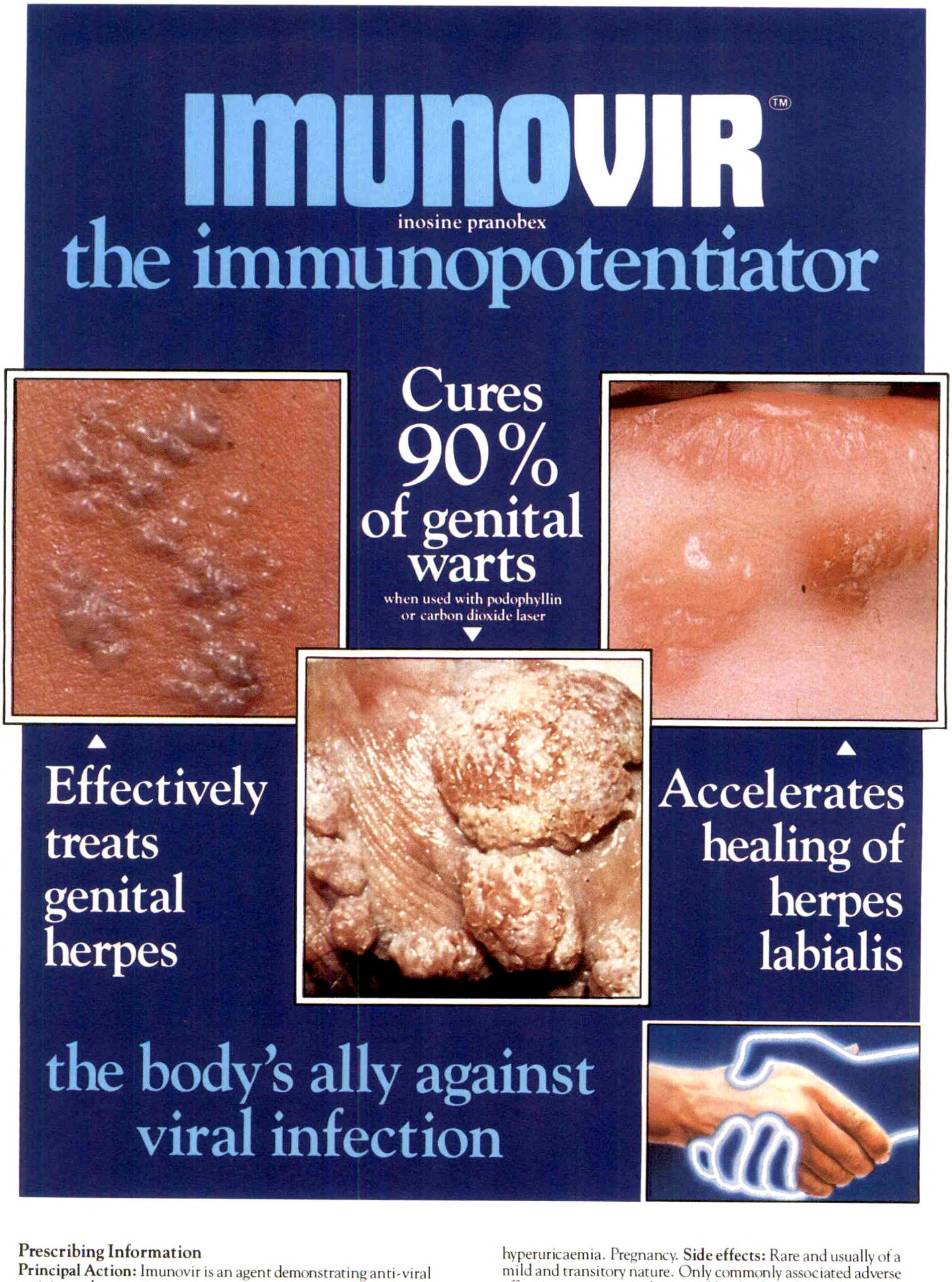
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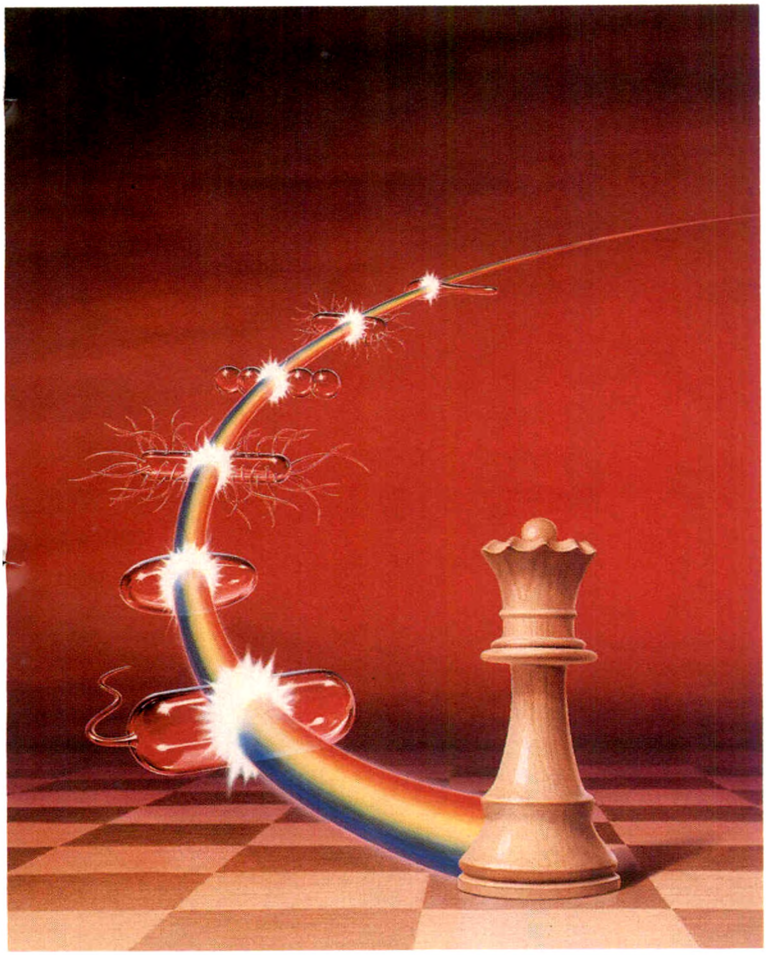

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References

1. Pipril Product Information Book. 2. Limson B.M., *et al.*, Proc. 11th Int. Congr. Chemotherapy, 1979, **1,** 297-299. 3. Prince, A., *et al.*, Proc. 11th ICC and 19th ICAAC, 1979, 295-296. 4. Marlin, G.E., *et al., J.Int.Med.Res.*, 1981, **9,** 268-273. 5. Valenti, S., *et al., Curr. Ther. Res.*, 1983, **33** (5), 745-750. 6. George, C.R.P., and Guinness, M.D.G., *Med. J. Aust.*, 1981, **1,** (1), 36-37. 7. Hoogkamp-Korstanje, J.A.A., *et al., J. Antimicrob. Chemother.* 1981, **8,** 101-106. 8. Viollier, A.F., *et al.*, 2nd Int. Symp. Infec. Immunocomp. Host 1983, 172-174. 9. Sanders, C.C., *J. Antimicrob. Chemother.*, 1984, **13,** 1-3. 10. Minami, S., *et al., Antimicrob. Ag. Chemother.*, 1980, **18,** (3), 382-385.

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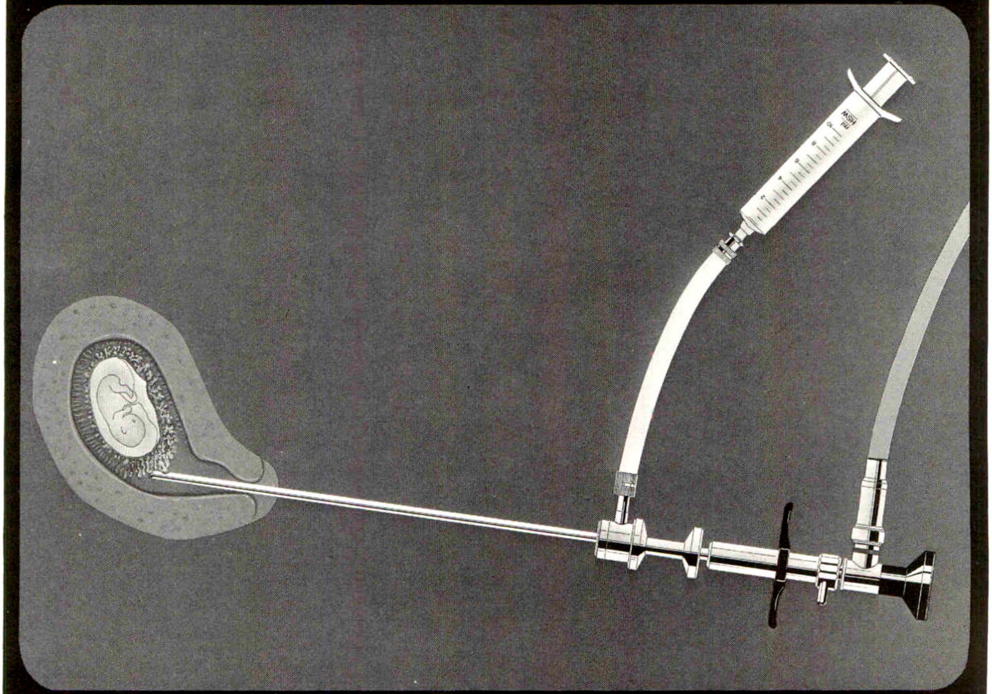

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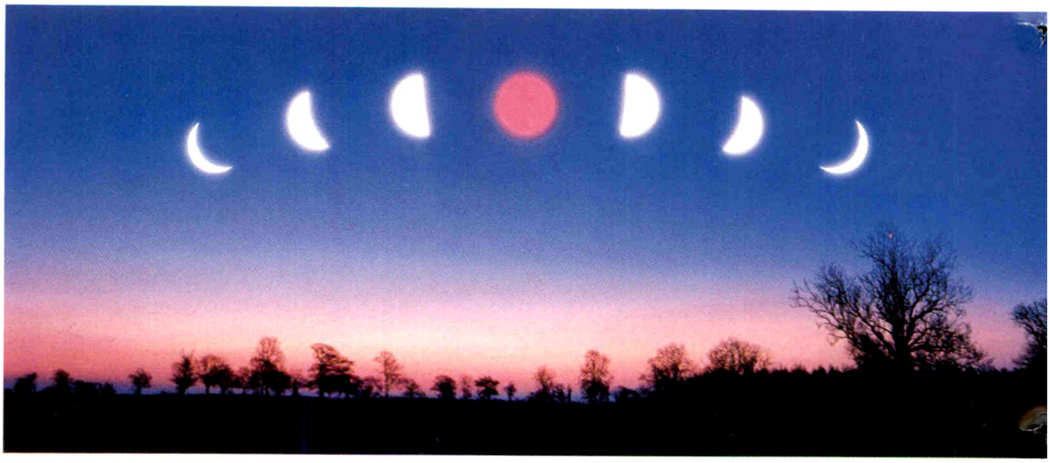

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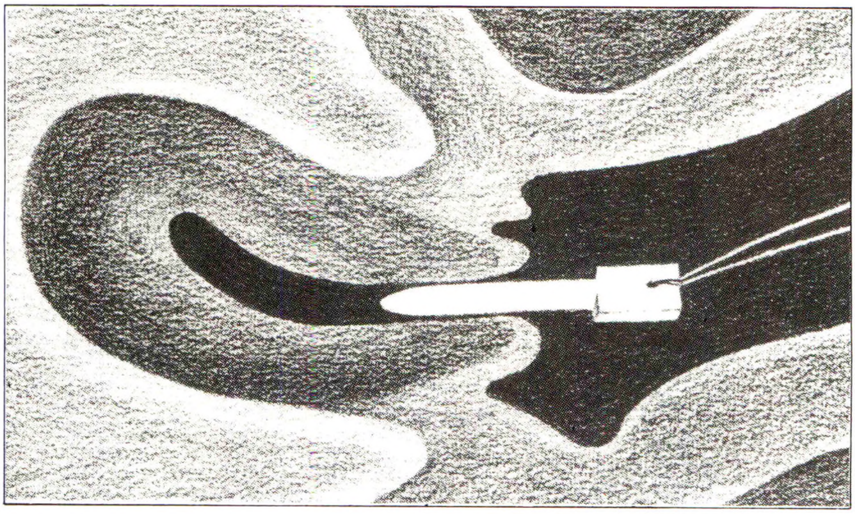

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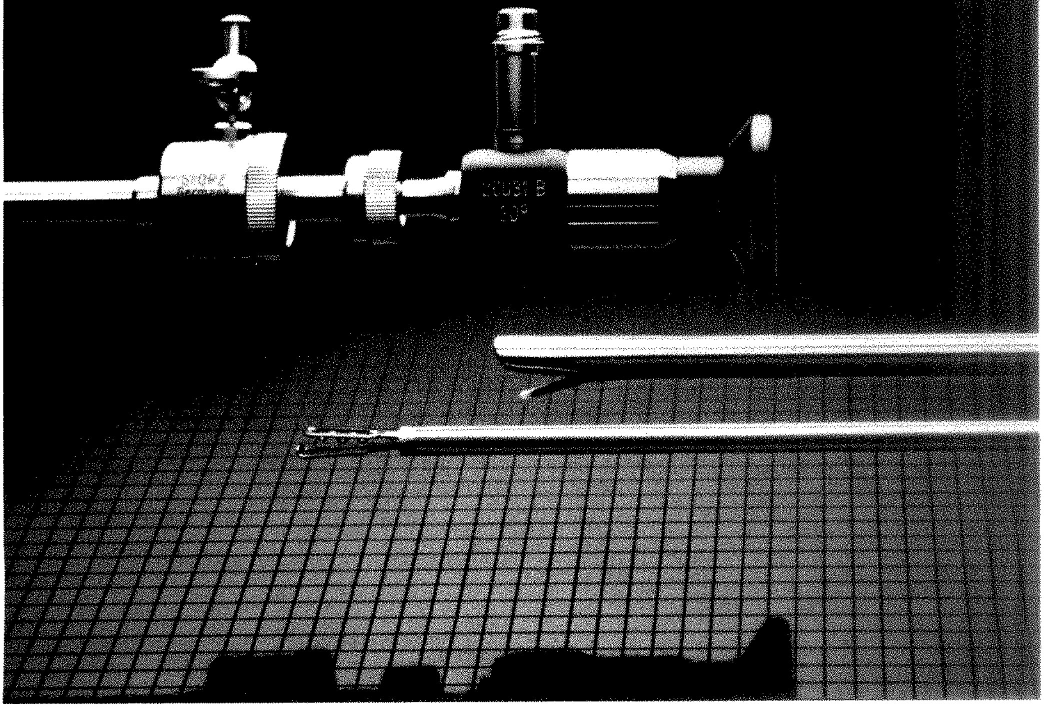

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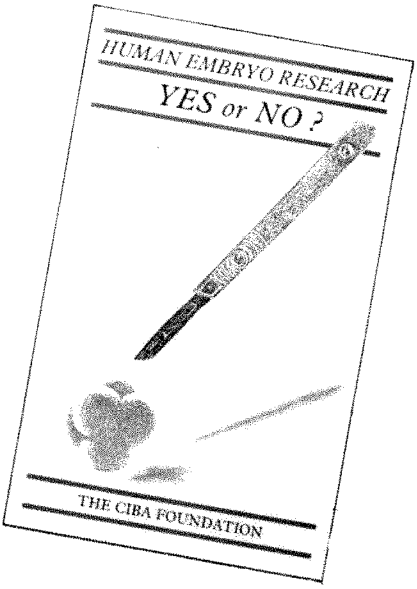

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COMMENTARY

How can we improve perinatal surveillance?

There was a time when obstetric care was judged largely by the maternal mortality rate. Since the dramatic fall in maternal mortality from the mid-1930s onwards, however, increasing attention has been directed to ways of improving the outcome for the fetus. Vital statistics published by the Registrar General continue to be used as a barometer of the success of maternity care; but the information derived from stillbirth and death certification has been limited, partly because of the design of the certificates, but also because of the quality of the information provided by doctors. National perinatal surveys were mounted in 1946, 1958 and 1970 (RCOG and the Population Investigation Committee 1948; Butler & Bonham 1963; Chamberlain *et al.* 1975) and these provided a detailed still photograph of events in a given week. However, apart from the 1958 survey, they included only small numbers of deaths and, in addition, they were both expensive to mount and slow to report. Locally produced hospital reports have not been an adequate substitute, both because they take no account of biases due to selective referrals to hospital for medical or geographical reasons, and again, because they are based on such small numbers of events.

Today's need is for continuous surveillance, preferably as part of a wider system of data collection. Such a system must be securely based, preferably on the obligatory registration of birth, so that all registrable births in populations defined geographically are included. If valid and useful information is to be produced for perinatal surveillance, however, clinicians must apply soundly based definitions in a standard manner and the resulting data must be assembled and analysed efficiently.

The first six papers in this issue of the Journal should help us to improve the quality of perinatel surveillance. The classification of perinatal deaths, which is so important for valid comparisons between populations, is the subject of the first two papers. In the first of these (p. 1204), Cole, Hey and Thomson have produced a revised version of the classification of death by 'obstetric cause' which was used by Baird & Thomson (1969) to analyse deaths in the 1958 British Perinatal Mortality Survey. This system attempts to reconstruct the sequence of events that led to the death so that obstetricians may seek to improve ways of dealing with whatever appears to be the triggering event. The revised version of the classification has been developed in the light of experience gained in the ongoing perinatal mortality surveys which have been established in Scotland (Scottish Health Service 1985) and the Northern Region (Northern Regional Health Authority Co-ordinating Group 1984).

To complement the classification of perinatal deaths by obstetric cause, Hey, Lloyd and Wigglesworth have, in the second article (p. 1213), produced a scheme for classifying fetal and neonatal deaths by clinico-pathological cause. The classification scheme proposed should help to minimize ambiguity in decisions about categorizing particular deaths and thus foster valid inter-regional comparisons.

In the third article (p. 1224), Macfarlane, Hey and Cole have outlined the form in which regions should present their data on perinatal mortality if they wish to take advantage of the Journal's offer to publish these (Chalmers 1985). Several regions would appear to be in a position to contribute relevant data for inter-regional comparisons (Mutch 1986). Hopefully, it will soon be possible to use this approach to examine the pattern of perinatal mortality across and within the whole of the United Kingdom.

Surveys of perinatal deaths too often lack denominators. An increasing amount of background information about total births to residents of a Health District or Region is available through the vital statistics generated by the Office of Population Censuses and Surveys

(OPCS). As the paper by Duley (p. 1233) illustrates, however, the quality of information provided by clinicians certifying stillbirths and neonatal deaths is still unnecessarily poor, partly because of the lamentable standard of perinatal pathology. The new forms of stillbirth and neonatal death certificates which came into use this year in England and Wales should help to improve the quality of certification. But this cannot happen without more effort by obstetricians, paediatricians and pathologists to ensure that valid information is forwarded to OPCS. The paper commenting on perinatal definitions (p. 1236) prepared by Chiswick on behalf of the Standing Joint Committee of the BPA and RCOG provides further illustrations of the need to exercise care in applying defining criteria if data permitting valid inter-regional comparisons are to be generated.

Improved certification and the application of reliable nomenclature are obviously crucial steps in the right direction, and regionally based enquiries are an important stimulus for these changes. But we also need a reliable means of collecting information on every maternity in the country. The only sources of information at present are vital statistics derived from birth certificates, but these do not include clinical information. Data collected at birth notification vary from district to district and so cannot be compared easily or aggregated at national level; and the 10% sampling of maternity hospital in-patients (Maternity HIPE) ceased at the end of last year.

The recommendations of the Steering Group on Health Services Information (the Körner Committee) have relevance here. In its first report the SGHSI (1982) made maternity an exception to its working rule to concentrate only on information required by health services managers. As the report noted, 'because of the interest and involvement of the relevant professional bodies, recommendations have been made about clinical data items to assist clinicians in reviewing the process of care (in the maternity services)'. Although this sounds promising, there have been problems. In particular, the Körner system is based on episodes of care received within a particular Health District. Obstetricians, midwives and paediatricians, however, need to know about the outcome of pregnancy, regardless of where the episodes of care took place. Just before the creation of the SGHSI, the RCOG and Northern Regional Health Authority had embarked on a revision of Maternity Hospital Activity Analysis which led to the design of the Standard Maternity Information System (SMIS). This system was designed to collect information retrospectively about a completed pregnancy, centring around the statutory notification of birth (Thomson & Barron 1980). SMIS also incorporated the means of producing (at intervals stipulated by the user) a fairly elaborate set of tabulations concerning mother and child. Although all the SMIS data items were incorporated into the Körner minimum and optional data sets, there are still no adequate provisions in the Körner recommendations for linking maternal and infant records about the same pregnancy (National Health Service 1985); nor has it been decided what tabulations should be produced by the system.

While health authorities in England grapple with the implementation of the recommendations of the 'Körner Committee', Scotland has already achieved a system for recording the outcome of every pregnancy with a viable outcome. Using such contemporary records, up-to-date reports on perinatal mortality, with geographical analysis, have been used to improve obstetric management (Scottish Health Service 1985). The Scottish Health Service has the advantage of an information service appropriate to central government with a close-knit maternity service. By contrast, there are 14 English regions, each of which has a population of 3–5 million, with widely differing social conditions and with a very variable degree of support for epidemiological services.

It should be possible to ease the transition to an improved basis for perinatal surveillance by advances in computer technology. The collection of information by form-filling is tedious, inaccurate, and offers the user no immediate feedback. Because it was unthinkable that such a method of data collection would be used to collect the Körner data sets, a number of centres were supported by the Computer Policy Committee to experiment with the installation of microcomputer networks in order to collect data directly from the scene of action for transmission to mainframe computers. The encouraging experience of Maresh and his colleagues at St Mary's Hospital, London, is reported on page 1239. Work is now going on which should make it possible for users of the Patient Administration System (PAS) designed by ICL to obtain the advantages of SMIS whilst satisfying the need for episodic data by managers (both clinical and administrative). The trouble is that, although Chairmen of RHAs have agreed to implement Kōrner by April 1987, and the maternity module by April 1988, there are signs that the installation of PAS, which is expensive in terms of skilled manpower as well as of money, will not cover all Health Districts in time to meet the deadline. Meanwhile, there is an uncomfortable hiatus with no national maternity data collection system for England since December 1985.

The maternity service has a well established reputation for clinical audit; now others are going to follow our example, more or less willingly. It will be up to obstetricians to make their voices heard in the Health Authorities where decisions are being made on the allocation of scarce computer resources. If we are seen to show a genuine concern for good quality information, backed up by locally organized enquiries into perinatal deaths, our case is irrefutable.

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Classifying perinatal death: an obstetric approach

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Summary. Consultation between the clinicians and epidemiologists responsible for the Perinatal Mortality Surveys in Scotland and in the Northern Regional Health Authority in England showed that the classification of perinatal death introduced more than 30 years ago by Sir Dugald Baird still retained its utility, but that unintentional differences in the way cases were being classified had threatened the validity of temporal or geographical comparisons. To overcome this problem an effort has now been made to define the main terms used in this classification more precisely. To preserve continuity, the main structure of the original groupings has been retained; but the opportunity has been taken to adjust certain minor groups in conformity with recent ideas, and also to modify definitions to take into account the greatly improved prognosis for babies of very low birthweight. Otherwise, it is thought that subclassification of the main groups offers a better method of exploring new hypotheses than any radical alteration of the main groups themselves.

The continuing national survey of perinatal mortality in Scotland (McIlwaine *et al.* 1985) and the comparable collaborative survey now in progress in the Northern Regional Health Authority (Northern Regional Health Authority Co-ordinating Group 1984), both regularly analyse the obstetric factors that lie behind each death using the classification first used in Aberdeen by Sir Dugald Baird and his colleagues (Baird & Wyper 1941; Baird *et al.* 1954). Consultation between the clinicians and epidemiologists responsible for the two surveys showed, however, that differences had developed in the way the classification was being used and interpreted north and south of the border. Differences had also developed between the way the classification had first been used by the original authors and in the way the classification was now being used in Scotland.

Many of the apparent discrepancies were resolved by reference to the definitive description of this classification by Baird & Thomson (1969). However, this description only appeared in print in the second of the two books reviewing the outcome of the 1958 British Perinatal Mortality Survey. Its existence is not widely known, and its accessibility is probably limited. We have therefore attempted to achieve brief consensus working definitions of the various terms used in this classification, retaining as far as possible the spirit of the guidelines first laid down by Baird & Thomson (1969), while acknowledging changes that have taken place more recently, especially in the prognosis for babies of very low birthweight. The present working definitions (Table 1) carry the support of the originators of this classification, and we hope they will prove of value to others currently engaged in setting up other surveys of perinatal mortality both in this country and abroad.

The present guidelines should be interpreted in the context of the statement by Baird & Thomson (1969) that the 'chief purpose of a classification of deaths is to assist prevention'; that postmortem findings may be inconclusive from this point of view because they indicate *how* but not *why* the baby died; and that the aim of the Aberdeen classification is to identify 'the

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factor which probably initiated the train of events leading to death'. To assist uniformity of classification a number of conventions must be utilized. Thus it is assumed that 'serious malformations take precedence over all other potential causes of death in a given case' and that isoimmunization 'takes precedence over all other [causes] except where there is malformation'. It is argued that, since such problems arise early in pregnancy, 'the child's life is prejudiced before most other causes of death have arisen'.

There is, therefore, a sense in which the various causes of death listed in Table 1 (and in Table 2) appear in a hierarchical order. Such an approach should not be used, however, if it leads to a conclusion which clearly infringes the cardinal rule that death should always be ascribed to the initial factor that set the baby's death in train. The test in doubtful cases is: 'would the average experienced obstetrician agree that this particular death might have been prevented by elimination of the cause selected'. This cause is frequently very different from the immediate cause of death, which may be a secondary complication of preterm delivery such as intraventricular haemorrhage or a nonspecific cause such as 'asphyxia'. A number of examples of the way the approach works out in practice are given in the Appendix.

Changes

The guidelines summarized in Table 1 differ from those laid down by Baird & Thomson

Table 1. Definition of the terms used in the 'Aberdeen' classification

Congenital anomaly: Any genetic or structural defect arising at conception or during embryogenesis incompatible with life or potentially treatable but causing death.

Isoimmunization: Death ascribable to blood group incompatibility.

Pre-eclampsia: Only significant pre-eclampsia, a diastolic blood pressure of 90 mmHg or more on two separate days after 20 weeks gestation (140 days) with significant proteinuria in the absence of existing hypertensive disease before pregnancy. The full definition of pre-eclampsia is the same as that given by the International Federation of Gynaecology and Obstetrics to the terms pre-eclampsia and eclampsia in the 9th Edition of the *International Classification of Disease* (ICD Codes 642.4–642.6).

Antepartum haemorrhage: Vaginal bleeding after 20 weeks gestation (140 days) whether revealed or not, excluding antepartum haemorrhage secondary to pre-eclampsia (which is classified under pre-eclampsia). Minor degrees of haemorrhage at the start of labour (a 'show'), and haemorrhage due to a cervical erosion or polyp should be ignored, but significant or recurrent bleeding of uncertain origin that is fairly closely followed by preterm labour should not be ignored.

Mechanical: Any death from uterine rupture and those deaths from birth trauma, or intrapartum asphyxia that are associated with problems in labour such as disproportion, malpresentation, cord prolapse, cord compression, or breech delivery in babies of 1000 g or more. If there is no evidence of difficulty in labour, deaths from asphyxia or trauma should be classified as 'Unexplained'. Antepartum deaths associated with cord entanglement in the absence of strong circumstantial evidence that cord compression caused death (e.g. fetal death soon after external version) should also be classified as 'Unexplained'.

Maternal disorder· Include maternal trauma (such as a road traffic accident), diabetes, appendicitis, and cardiac disease, etc, if severe enough to jeopardize the baby. Include significant renal disease or essential hypertension known to be present before pregnancy. Also include symptomatic and asymptomatic maternal infection when this results in the death of the baby.

Miscellaneous: Specific fetal and neonatal conditions only. Do NOT include conditions directly ascribable to prematurity or asphyxia before birth, because these deaths are attributable to the relevant underlying obstetric disorder. Include, however, specific fetal conditions (e.g. twin-to-twin transfusion) or neonatal conditions (e.g. inhalation of milk) where these are not directly ascribable to intrapartum anoxia or preterm delivery. Include, also, postnatally acquired infection, except in babies of less than 1000 g; here the reason for the low birthweight is the codable factor.

Unexplained: Deaths with no obstetric explanation, including unexplained antepartum stillbirths, deaths resulting from unexplained preterm delivery (including hyaline membrane disease, intraventricular haemorrhage, etc) and cases of intrapartum asphyxia or trauma if the baby weighed less than 1000 g at birth or delivery was unassociated with any obvious mechanical problem. Cases should be subclassified into those babies weighing 2500 g or more and those of less than 2500 g at birth.

Unclassifiable: Cases where little or nothing is known about pregnancy or delivery only. Use this category as sparingly as possible.

(1969) in a number of minor but important respects.

Pre-eclampsia

The current internationally agreed definition (FIGO 1981) differs only slightly from that originally used by Baird *et al.* (1954) for toxaemia. It is recommended, therefore, that the term pre-eclampsia should be used for 'pregnancy-associated hypertension which appears for the first time after the 20th week associated with more than a trace of proteinuria or symptoms commonly found in the clinical syndrome of pre-eclampsia (headache, epigastric pain, visual disturbance, extensive generalized oedema), in a subject with no previous history of hypertension'. 'In this context hypertension is defined as a diastolic level of 90 mmHg (12 kPa) or more, taken under reasonably standard conditions with the Korotkoff phase 4 being used to define the diastolic pressure (i.e. muffling)'. Hypertension present before pregnancy or hypertension developing as a consequence of known renal disease before pregnancy is classified as a 'Maternal disorder'.

Antepartum haemorrhage

We propose to retain the assumption that haemorrhage occurring in association with severe pre-eclampsia is 'caused' by the pre-eclampsia—that is that deaths in which both conditions were present should be classified as due to pre-eclampsia. Those who wish to make different assumptions (e.g. that antepartum haemorrhage is not causally associated with pre-eclampsia) may investigate the matter by subclassification. Note also that the diagnosis of antepartum haemorrhage has to be employable from 20 completed weeks (140 days) gestation, for reasons stated below (see Discussion).

Mechanical causes

Baird & Thomson (1969) defined an extremely small baby as one weighing less than 4 lb (1815 g); in such cases, the condition causing the low birthweight—if obvious—was to be given priority over difficult labour or infection, on the grounds that it was the baby's size and immaturity that accounted for the child's vulnerability to trauma or infection. The prognosis for babies of very low birthweight has improved so much since 1969 that it now seems right to lower the threshold and to express it metrically. We suggest that the threshold should be lowered to <1000 g.

Miscellaneous

'Infection of the foetus or infant' was a separate category in the original classification. In the 1958 Perinatal Mortality Survey (Baird & Thomson 1969), however, only 1·1% of deaths were attributed to infection from the evidence of the clinical records, and it seems illogical to group cases where infection of the baby arose from maternal infection (including asymptomatic infections present during labour) with cases of primary neonatal infection after delivery. We therefore propose to group primary maternal infections with 'Maternal disorders', and primary (postnatal) infections with other 'Miscellaneous', largely neonatal, conditions. Numbers are too small to have an appreciable effect on comparisons with vital statistics compiled on the original basis. If, nevertheless, infections are thought to be worthy of further study they can be subclassified or isolated from the groups with which they are merged and studied in their own right.

Unexplained

The original classification divided 'deaths of uncertain origin' into 'mature' and 'premature' by weight (over 2500 g and 2500 g or less at birth). This subdivision remains important, not only for the sake of historical continuity, but because it has been shown repeatedly that the two groups of deaths have different epidemiological characteristics with different implications for prevention. We therefore propose to retain the subdivision, but to modify the dividing line in accordance with modern usage (WHO 1977), i.e. '2500 g or more' and 'under 2500 g'. This apparently trivial change may affect more babies than might be supposed, because most babies are only weighed to the nearest 10 g at birth.

Subclassification

Baird & Thomson (1969) listed several subdivisions of each of their main categories. Apart from the subdivision of 'unexplained' deaths by birthweight, and probably the division of congenital defects into those of the nervous system and others, we are not convinced that the original suggestions have proved sufficiently useful to justify their incorporation into routine vital statistics. It is, nevertheless, important that new ideas should be tested by methods that, whenever possible, permit direct comparisons to be made with past experience. This can be best achieved by using subclassifications of the main groups. The subclassifications suggested in Table 2 have been inserted to indicate how epidemiological experiment and innovation may be introduced without impairing the usefulness of the main classification. We have not attempted to reach any consensus between the Scottish national survey and the English regional survey on such further subclassification. Indeed, there are probably quite strong arguments for not demanding uniform subclassification at the present time but rather encouraging experiment and innovation.

The separation of babies with neural tube defect from other deaths due to malformation makes sense from an epidemiological and also from a clinical point of view given the techniques now available for detecting most defects antenatally (note that death from a neural tube defect is not synonymous with *all* death from

Table 2. Option for the further subclassification of perinatal death

Classification of Baird & Thomson (1969)	Current terminology	Possible subclassification*
Malformation	Congenital anomaly	Neural-tube defects. Other anomalies.
Serological incompatibility	Isoimmunization	Due to the Rhesus (D) antigen. Due to other antigens.
Toxaemia	Pre-eclampsia	Without APH. Complicated by APH.
Antepartum haemorrhage (without toxaemia)	Antepartum haemorrhage (APH)	With placenta praevia. With placental abruption. APH of uncertain origin.
Mechanical	Mechanical	Cord prolapse or compression with vertex or face presentation, Other vertex or face presentation. Breech presentation. Oblique or compound presentation uterine rupture, etc.
Maternal disease	Maternal disorder	Maternal hypertensive disease. Other maternal disease.
Infection of the fetus or infant		Maternal infection.
	Miscellaneous	Neonatal infection.
Miscellaneous		Other neonatal disease. Specific fetal conditions.
Uncertain { Mature Premature	Unexplained ≥2·5 kg Unexplained <2·5 kg	
Unclassified	Unclassifiable	

* Further exploratory subclassification is made easier if each factor contributing to the death is coded using the ICD system.

CNS malformation). The separation of maternal hypertensive disease from other maternal illness is of value to those interested in all hypertensive disease in pregnancy whether associated with any detectable abnormality before pregnancy or not, and the separation of isoimmunization due to Rhesus D antigen from all other isoimmunization has similar clinical utility. The presence of a separate subcategory for maternal infection and for neonatal infection makes it possible to compare current trends in the prevalence of primary infectious death with previously collected data using the 1969 version of this classification. In other respects the subclassification offered in Table 2 follows that outlined by Baird & Thomson (1969).

Comment

The experience of three decades has shown that the Aberdeen classification of perinatal death shows remarkably few signs of obsolescence. Different assessors can classify a series of death with considerable unanimity, provided close attention is paid to the published definitions and 'working rules'. We have found that if a group of experienced clinicians are asked to classify the same cases for a second time after an interval, more than 99% of the cases are classified in the same way, while differing groups reach similar conclusions in 97% of cases submitted for assessment as long as they have a copy of these 'ground rules' before them. Good clinical records are highly desirable, and an autopsy report may be invaluable, but the classification can yield useful statistics even where the notes are imperfect and when no autopsy is undertaken. The main groups specified are intended to show broad trends with time or differences between samples. As Baird & Thomson (1969) noted: 'It may in some circumstances be better to classify a high proportion of deaths with reasonable certainty than to use such a detailed classification that a substantial proportion of deaths cannot be classified at all'. Furthermore, if trends and differences are to be revealed, it is essential to minimize changes and differences of method.

We believe that the present definitions, while modernizing the Aberdeen classification in several respects, are sufficiently consistent with the original specification to enable comparisons to be made with considerable confidence. We also believe that the same approach that has been used to study and classify perinatal death for many years should now also be used to study late neonatal death, though we doubt whether the Aberdeen classification can be used realisticaly to classify babies who die more than 4 weeks after birth. More importantly, the classification should also be used with those babies who are born dead at 22–27 weeks gestation (Whitfield *et al.* 1986) since, in line with the recent RCOG Report (1985), we believe that 'a record should be kept of all babies born alive or dead at 22 weeks (154 days) gestational age or, if born earlier, weighing 500 g or more'. Any definition of antepartum haemorrhage must therefore, for consistency, be capable of being made by the 21st week of pregnancy when used in the context of this classification (whatever the current generally agreed international definition of this term when used in connection with ICD code 641).

Finally, we believe there is a case for a parallel fetal or neonatal classification of every perinatal death conducted in tandem with this maternal analysis, and that dual classifications, although cumbersome, are becoming increasingly important and informative as paediatric care comes to occupy a more central role in the management of most ill babies at birth. Such a concept seems to be supported by the World Health Organization's proposal for a special perinatal death certificate (WHO 1977) containing statements both about the various diseases or conditions in the fetus or infant and also about the various maternal diseases or conditions affecting the fetus or infant. Indeed, revised stillbirth and neonatal death certificates, in line with these recommendations, have just come in to use from the beginning of 1986 in England and Wales (but not in Scotland). Experience has shown, however, that even simple paediatric clinico-pathological classifications such as those proposed by Bound *et al.* (1956) or Wigglesworth (1980) are capable of being interpreted in a very variable manner by different clinicians in the absence of any agreed 'ground rules' of the type developed by those first involved in the introduction of the Aberdeen classification. Those currently involved in the Scottish National and Northern Regional surveys have therefore attempted to develop some 'ground rules' for such a second classification, and these are outlined in the companion paper by Hey *et al.* (1986) on p. 1213 of this issue.

Acknowledgments

The first two authors were authorized to write this statement on behalf of the Scottish Perinatal Mortality Committee and the Northern Regional Co-ordinating Group and the third author was invited to join them as a representative of the group who designed the original classification. We are grateful to Sir Dugald Baird for reading and commenting on the paper in draft.

The current Members of the Scottish Committee are Professor Sir Malcolm Macnaughton (Chairman), Dr S. Cole, Dr. A. Gibson, Dr M. Hennigan, Dr R. C. Howat, Dr D. W. Holton, Dr D. J. Loyd, Dr G. M. McIlwaine, Dr N. Patel and Miss A. N. Taylor.

The Co-ordinating Group responsible for the Northern Regional survey currently consists of Dr R. G. Welch (Chairman), Mr S. L. Barron, Mr C. H. W. Bullough, Dr E. N. Hey, Mr R. Layton, Mr R. A. McNay and Dr D. Morris.

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Appendix

It may help to illuminate the general principles with actual examples of the problems occasionally encountered when trying to develop a consistent unitary classification.

Case A

A healthy primigravid woman develops progressive hypertension (blood pressure 140/95 mmHg) and moderate proteinuria at 26 weeks gestation. Three weeks later spontaneous preterm breech labour develops while she is an antenatal inpatient. The cervix is still closed but no fetal heart can be heard on admission to the delivery area. Labour progresses rapidly and cord prolapse is diagnosed at full dilatation shortly before a slightly macerated baby is stillborn weighing 1·3 kg after a 4-h labour. There is no retroplacental clot and postmortem examination is non-contributory except that it reveals a small high muscular ventricular septal defect.

Comment

The ventricular septal defect is not the sort of problem that would compromise the fetal circulation and there were no other detectable congenital abnormalities so it seems wrong to ascribe death to the congenital anomaly, although this was the convention followed in 1969. It would have been reasonable to ascribe death to cord prolapse had there been evidence that the baby was still alive at the start of labour, but the fetal heart was not detected in labour and the baby was slightly macerated at birth after a labour lasting only 4 h, so it can reasonably be assumed that the baby was dead before labour began. In the circumstances, therefore, this antepartum stillbirth is classified as being due to pre-eclampsia.

In passing it should be noted that death would have been classified as Mechanical (breech) and not as Mechanical (cord prolapse) had the baby been alive at the time the cord prolapse occurred using the ground rules developed by Baird & Thomson (1969) as summarized in Table 2.

Case B

A primigravid woman with chronic pyelonephritis develops moderate medically controlled hypertension during pregnancy. She is then delivered electively by caesarean section of a baby weighing 2·3 kg after generalized fetal hydropic changes are identified on ultrasound at 31 weeks gestation. There is no relevant family history, no evidence of infection, no sign of serological incompatibility and the chromosomes are normal but there is circumstantial laboratory evidence of chronic fetal anaemia due to feto-maternal bleeding. The baby responds to an exchange transfusion but requires ventilatory support from birth and dies from sudden complicating staphylococcal septicaemia when 5 days old. A postmortem confirms that there is no structural heart disease or other congenital malformation.

Comment

There is no evidence of isoimmunization or of congenital or genetic abnormality. There is underlying maternal ill health but nothing to suggest that this was related to the baby's death and, while the death was caused by sudden septicaemia, this was clearly not the problem that 'set the baby's death in train'. While the cause of the fetal hydrops is not known for certain the baby did have a 'specific fetal condition' and it seems right therefore to classify this as a Miscellaneous (fetal) death.

Case C

A woman who has had two healthy children born at term weighing over 4 kg has a further uneventful pregnancy before going into spontaneous labour at 37 weeks gestation. The fetal heart stops unexpectedly towards the end of the first stage of labour and a baby of 1·9 kg is born spontaneously by the vertex as a fresh stillbirth after an easy second stage lasting just 15 min. The umbilical cord contains a true knot. Death is ascribed to cord compression by the obstetrician, but autopsy reveals a major tentorial tear with extensive blood in the posterior fossa as well as features of intrapartum asphyxia.

Comment

Death due to tentorial damage is rare before the second stage of labour but, whatever the timing of the death, the lack of any disproportion or malpresentation makes death due to Mechanical difficulty an inappropriate obstetric diagnosis even with convincing autopsy evidence of tentorial trauma. Neither is a mechanical death due to a knot in the cord likely in the first stage of labour. A fetal or neonatal classification would ascribe death to intrapartum asphyxia with or without trauma depending on whether the tentorial damage was thought to have occurred before or after death but, from an obstetric point of view, this death has to be classified as Unexplained: birthweight <2·5 kg. In the 1969 classification the terminology would have been 'Uncertain: premature by weight' but this terminology has lost its currency and is best avoided. The baby is a term baby of low birthweight making this a case where some further experimental subdivision of the classification summarized in Table 2 might be of value. Many would feel that intrauterine growth retardation had left this baby vulnerable to intrapartum stress.

Case D

A woman who has two healthy children becomes pregnant shortly after having a cone biopsy for cervical carcinoma *in situ*. There is evidence of cervical incompetence complicated by premature rupture of membranes at 29 weeks gestation and continuous loss of amniotic fluid until spontaneous preterm labour supervenes 5 weeks later. A baby of 2·1 kg with talipes and features suggesting oligohydramnios is born who dies with unrelieved cyanosis and a terminal pneumothorax after 8 h despite all available respiratory support, and an autopsy shows immature severely hypoplastic lungs (combined weight 23 g).

Comment

Death here is clearly caused by pulmonary hypoplasia but this would seem to be an acquired problem secondary to chronic oligohydramnios rather than congenital in origin. Were the cause of the premature rupture of membranes unexplained the death would have to be classified as Unexplained: birthweight <2·5 kg but since in this case it is clearly a secondary complication of a recognizable maternal problem the more appropriate classification is Maternal disorder. (Preterm labour due to subseptate uterus would be classified the same way, but idiopathic cervical incompetence would normally be classified as Unexplained; while such fine distinctions are somewhat arbitrary, what really matters in the present context is consistency of approach.)

Case E

A healthy primigravid woman has a pregnancy complicated by episodes of unexplained painless vaginal bleeding at 17 and 22 weeks. All seems well with the pregnancy on review at 31 weeks and sonar examination reveals a normally situated fundal placenta, but rapid progressive labour without any further blood loss develops 5 days later and a baby of 910 g is born with a unilateral cleft lip and palate. The uterus is not tender and there is no retroplacental clot. The baby dies despite attempted resuscitation within 30 min. Postmortem examination fails to reveal any other structural abnormality except a minor degree of syndactyly.

Comment

There must be a suspicion that this was a blighted pregnancy almost from the outset, but there is no evidence of placenta praevia or placental abruption, and the only episodes of antepartum bleeding are not 'fairly closely followed by preterm labour' so it seems wrong to classify this death as due to antepartum haemorrhage. The baby was small-for-dates and had at least two separate congenital abnormalities at birth but neither of the defects are even remotely likely to cause death had the child been liveborn. The death has to be classified, therefore, as Unexplained: birthweight <2·5 kg. Had the clinical features pointed to some syndrome (such as a chromosomal disjunction abnormality) known to be associated with an increased chance of antepartum stillbirth it would have been entirely right to ascribe death to Congenital anomaly.

Case F

A woman with anti-c rhesus antibodies has labour induced at 36 weeks and gives birth to an abnormal looking 2·6 kg baby with obvious haemolytic anaemia (cord Hb 9 g/dl). Six hours after an exchange transfusion is undertaken the baby develops severe necrotizing enterocolitis dying of surgical complications 4 h after total colectomy.

Comment

The clinicians saw the necrotizing enterocolitis as a complication of the exchange transfusion making this a death due to Isoimmunization (due to an antigen other than the usual D rhesus antigen) rather than to Miscellaneous causes (neonatal infection). However, at autopsy it became clear that the baby had holoprocencephaly, a severe CNS defect incompatible with long-term survival. Even though this abnormality did not actually cause the death in this case, it seems right to classify this death as due to Congenital anomaly because of the guideline that 'malformation takes precedence over all other potential causes of death'. Holoprocencephaly is, incidentally, an example of a congenital CNS defect that is not a neural tube defect.

Case G

The rather decomposed body of a baby of 2·2 kg was found still attached to a placenta in a plastic bag on a town allotment. Postmortem examination fails to comment on the baby's gestational maturity and fails to find any cause for death but suggests that the baby must have died at least 24 h before delivery.

Comment

Too little is known about this baby to make classification possible. Had there been evidence that an otherwise healthy full-term baby had died from 'want of attention at birth' it would have been more satisfactory to classify the death as Unexplained because of the guideline that deaths should only be left unclassified if it is quite impossible to make an informed guess about the probable cause of the baby's death. Had there been clear evidence that the baby died of exposure after being born alive on the other hand, it might have been more appropriate to classify this as a Miscellaneous (neonatal) death.

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Classifying perinatal death: fetal and neonatal factors

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Summary. It has been common practice in the United Kingdom for more than 30 years to classify perinatal deaths according to the maternal condition that initiated the events that led to death. However, such an approach tends to ignore the baby as an individual in his or her own right. The need for an additional classification that identifies the pathological processes occurring in the *baby* in every perinatal death has long been recognized, and the classification adopted in the 1958 British Perinatal Mortality Survey has now been revised with this need in mind.

The most commonly used approach to the classification of perinatal death in the United Kingdom is that first adopted by Baird & Thomson (1969), but this concentrates on maternal factors and takes little account of the baby as a separate individual, the clinico-pathological processes within the baby, and the way they contribute to, and help to explain, the baby's death.

Bound *et al.* (1956) published such a classification based on autopsy findings although they claimed no originality for their proposal, and indeed justified it, in part, by acknowledging that their proposed groupings were only those already widely used by others interested in this issue in many different parts of the world. This same classification, with minor modifications, was later employed to analyse the results of the 1958 British Perinatal Mortality Survey and the section of the book reporting the main autopsy findings contains useful working definitions of the various terms and categories used (Butler & Bonham 1963). Other slightly different classifications have been proposed from time to time (cf. Fairweather *et al.* 1966) but none seem to have displaced the primacy of the classification first formally proposed by Bound *et al.* (1956) and adopted by Butler & Bonham (1963).

The classification was designed for use in cases where pathology had been verified by autopsy, a condition that may only apply to about two-thirds of all perinatal deaths in Britain, of which less than a fifth are at present undertaken by pathologists with special skills in perinatal pathology (Golding 1982). Consequently it has been suggested that a simpler grouping may be preferable, based on externally observable features augmented by those ascertained from the history (Wigglesworth 1980). However, experience in the Northern region and separately in the North West Thames region has shown that with the use of modern diagnostic procedures, such as the range of imaging techniques now available both perinatally and in the neonatal period, quite sophisticated pathological diagnoses may be possible, even in infants who never come to autopsy. By redefining some of the categories used by Butler & Bonham (1963) and judicious editing we think it is now possible to construct a series of primary pathological groups into which most cases can be classified even in the absence of autopsy information. For epidemiological purposes, where the number of deaths is relatively small, or where less detailed information is available, a simpler series of broader categories may remain more appropriate.

Changes

The working definitions we have used for the various categories in the currently proposed classification are summarized in Table 1, and the extent to which the classification we are now proposing differs from that used by Butler &

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Table 1. Definition of the terms used when classifying the main fetal and neonatal factors involved in any perinatal death

Congenital anomaly. Any genetic or structural defect arising at conception or during embryogenesis incompatible with life or potentially treatable but causing death Separate out deaths associated with a neural tube defect and death caused by a chromosomal, cardiac or renal abnormality from deaths due to other miscellaneous or multiple abnormalities.

Isoimmunization: Deaths due to feto-maternal blood group incompatibility.

Asphyxia before birth (whether the baby is stillborn or not): Specify whether the insult originated before or during labour. All non-malformed stillborn babies are arbitrarily classified as dying of asphyxia unless death is due to a specific recognizable condition such as idiopathic hydrops fetalis, twin-to-twin transfusion etc, or there is evidence of malformation, isoimmunization, trauma or infection. It would be assumed that asphyxia developed during labour unless there is reasonable evidence to the contrary if the baby was alive when labour started.

Birth trauma Death during or after birth due to rupture of the liver, splenic avulsion, or due to serious damage to the falx, tentorium, great cerebral vein or cervical spine during delivery. Where there is clinical or postmortem evidence of severe fetal asphyxia, death should be ascribed to asphyxia before birth (see above) unless it is clear that trauma is the more important factor.

Severe pulmonary immaturity: Babies with structural immaturity of the lung so gross as to render sustained ventilatory support unsatisfactory from the outset. Such babies are almost always less than 27 weeks gestation at birth.

Hyaline membrane disease (HMD): Death due to pulmonary immaturity or surfactant deficiency Specify whether there was significant periventricular bleeding (or infarction) or secondary infection as well

Intracranial haemorrhage: Separate deaths due to intraventricular or periventricular haemorrhage (and/or infarction) from other intracerebral haemorrhage (such as subdural or subarachnoid bleeding. Exclude intraventricular and periventricular haemorrhage associated with potentially lethal HMD, and other haemorrhage secondary to trauma or asphyxia before delivery (see above).

Infection (including necrotising enterocolitis): Include antepartum as well as postpartum infection but exclude infection secondary to treatment for HMD. Separate deaths from necrotising enterocolitis from other deaths, and indicate, in the remaining cases, whether the infection was thought to have been acquired before the onset of labour, during delivery, or after birth. Specify site and organism.

Miscellaneous Death due to other specific fetal and neonatal conditions. Specific fetal conditions include tumours, unexplained hydrops fetalis and death due to the twin-to-twin transfusion syndrome. Specific neonatal conditions include aspiration of milk or gastric contents, unexplained pulmonary haemorrhage, pulmonary hypoplasia due to prolonged loss of amniotic fluid (primary hypoplasia being classed as a malformation), persistent transitional circulation (in the absence of underlying aspiration or surfactant deficiency), and blood loss unassociated with trauma.

Unclassified or unknown: Other inadequately documented deaths, unattended deliveries, unexpected and unexplained cot deaths

Bonham (1963) is outlined in Table 2. The main differences are as follows.

Congenital anomaly

Extensive experience in the Northern region confirms that clinicians do not usually have any difficulty in deciding which neonatal deaths fall into this category: it may be more difficult, however, to decide whether a stillborn baby has died *of* a malformation or merely *with* a malformation. If the defect was one that would have inevitably caused death after birth anyway (such as bilateral renal agenesis), classification is easy because the anomaly was clearly 'incompatible with life' even though it is difficult to explain why the defect caused death before birth. It may be equally difficult to explain why an exomphalos should cause death before birth and an isolated exomphalos would not, by itself, usually cause death after birth with skilled surgical treatment. However, it is known that there is an increased risk of stillbirth in such babies; we therefore accept these deaths as being 'due' to congenital anomaly. This would not generally be true for a baby with an isolated segmental jejunal atresia; note, however, that if polyhydramnios were to cause death as a result of premature labour or if late diagnosis or a complication of surgical treatment were to cause death in such a baby, it would be appropriate to ascribe death to the known congenital anomaly since, even though the atresia was potentially treatable, it did, in this instance, cause death.

Table 2. Classifying perinatal death: fetal and neonatal factors

Classification of Butler & Bonham (1963)	Current classification	Suggested sub-classification*	Category
Congenital malformation	Congenital anomaly	Chromosomal defect	1
		Inborn error of metabolism	2
		Neural tube defect	3
		Congenital heart disease	4
		Renal abnormality	5
		Other malformation	6
Isoimmunization	Isoimmunization		7
Antepartum death with autopsy evidence of anoxia	Antepartum asphyxia		8
Antepartum death without autopsy evidence of anoxia			
Intrapartum death with autopsy evidence of anoxia	Intrapartum asphyxia		9
Intrapartum death with autopsy evidence of anoxia and trauma			
Intrapartum death without autopsy evidence of anoxia or trauma			
Cerebral birth trauma	Birth trauma		10
Neonatal death (no autopsy abnormality)	Pulmonary immaturity		11
Hyaline membrane	Hyaline membrane disease (HMD)	HMD	12
		HMD with IVH	13
		HMD with infection	14
Intraventricular haemorrhage (IVH)	Intracranial haemorrhage	Intraventricular haemorrhage	15
		Other intracranial bleeding	16
Pulmonary infection	Infection	Necrotizing enterocolitis	17
		Antepartum infection	18
Extrapulmonary infection		Intrapartum infection	19
		Postpartum infection	20
Massive pulmonary haemorrhage	Miscellaneous		21
Miscellaneous			
No necropsy	—	—	
—	Unclassified or unknown	Cot death	22
		Unattended delivery	23
		Undocumented or unclassified	24

* Further detailed subclassification is rendered much easier if each congenital anomaly and each factor contributing to the death is separately coded using the ICD system.

Some congenital anomalies fall uncomfortably between the two extremes already referred to. Here it may be necessary to take all the available information into account before making the most informed judgement possible. Thus in Turner's syndrome it may be necessary to consider each case on its merits. If a girl with 45X is found to have extensive cystic hygromata in early fetal life, late fetal death or stillbirth is really extremely likely. If, on the other hand, 45X is recognized on a routine amniocentesis and major structural abnormalities are absent, one would not expect the baby to be stillborn.

Problems arise where several separate abnormalities are found after birth in a stillborn baby all of which (taken singly) are relatively minor, and none of which (in themselves) can be said to 'explain' the death. We have taken the view that it is not unreasonable to classify death as due to a 'congenital anomaly' when three or more such abnormalities are found, even though we can not explain precisely what was going on before birth, accepting that the identified anomalies, though minor, may be the only visible manifestation of a much more severe (but unrecognized) syndrome or fetal disorder (particularly where there is associated evidence of fetal growth retardation).

There has always been a common policy to include babies dying with a recognizable chromosome defect with other babies dying of a structural abnormality (since many of these babies look abnormal). In the past, however, babies with a genetically determined disease (such as cystic fibrosis) or an inborn error of metabolism (such as galactosaemia) have often been classified as dying of a 'specific fetal or neonatal condition' (Table 2 category 21). Such a dichotomy seems illogical; it will also become increasingly inappropriate as techniques are developed for diagnosing more of these conditions antenatally. We therefore classify all single gene defects as Congenital anomaly.

We have grouped babies with a severe deformation of early onset (such as a major amniotic band anomalad) with the other perinatal deaths that are unequivocally due to problems 'arising at conception or during embryogenesis'. However, Butler & Bonham (1963) included deaths due to deformation (such as an extrauterine pregnancy or pregnancy in one horn of a bicornuate uterus) in the 'Miscellaneous' category along with congenital tumours and harmartomas. It is often difficult to decide whether a case of arthrogryposis or congenital porencephaly should be classified as a congenital anomaly or as a miscellaneous death; we have classified these conditions as Congenital anomaly unless there is clear evidence that the damage occurred after the fourth month of pregnancy. Babies with isolated pulmonary hypoplasia present a special problem. Where there is reasonably strong retrospective evidence of prolonged loss of amniotic fluid and severe oligohydramnios we would classify these deaths as due to a recognizable 'specific fetal or neonatal condition', but other cases have to be classified as congenital in origin

Since malformation now accounts for between a quarter and a fifth of all perinatal death, there is probably a case for further sub-dividing this major category of perinatal loss (see Table 2).

Antepartum and intrapartum asphyxia

A unique feature of the 1958 Perinatal Mortality Survey was the trouble taken to ensure that almost every baby that died was subjected to detailed examination by one of a small group of experienced pathologists working to a common study protocol. Detailed autopsy information was available on 93% of all the perinatal deaths occurring in March. In addition to this, histological samples from each perinatal death were available for review by a central panel in 87% of all the babies. The pathologists responsible for the analysis of the deaths in the 1958 survey therefore felt justified in separating out those stillbirths where there was autopsy evidence of asphyxia (small haemorrhages in the visceral and parietal pleura in the chest, congestion of the liver, spleen and adrenal medulla, and/or meconium or amniotic debris in the bronchi or alveolar ducts) from those where there was no such evidence. Such a distinction is, however, difficult to sustain except in the context of a research study with consistent, high quality, autopsy information including mandatory pulmonary histology. It may also be helpful to separate out cases where death from asphyxia has clearly been caused by placental abruption as a special sub-category, but this approach is not, of course, necessary if each perinatal death is subjected to dual classification (Cole *et al.* 1986).

Note that we have preferred the term asphyxia to anoxia or hypoxia (although hypoxia seems to be the term now generally preferred in obstetric circles) because asphyxia implies interference with all gaseous exchange and not just lack of oxygen. The problems encountered after birth are usually thought to be due to the synergistic effect of oxygen lack, carbon dioxide retention and the resultant mixed secondary acidosis, and we believe that interference with gaseous exchange before birth may also, on occasion, involve some variable combination of these factors.

Birth trauma

The 1958 Perinatal Mortality Survey only included deaths due to *cerebral* birth injury confirmed at autopsy. Evidence of cervical damage was not always looked for, and cases of haemoperitoneum associated with subcapsular liver haematomata were grouped with deaths due to asphyxia. We have preferred to include these deaths with other deaths due to trauma. The 1958 survey also separated deaths in which there was evidence of asphyxia as well as trauma from those where there was no autopsy evidence of asphyxia. We have found such a distinction difficult to sustain on the basis of routinely available post mortem evidence, although it often appears almost deceptively easy to make such a distinction when the autopsy findings are read in the context of the available clinical narrative. Deaths with evidence of birth trauma are now only about a tenth as common as they were 30 years ago in British obstetric practice; as they are so rare it does not seem appropriate to retain a separate category for deaths with evidence of both trauma and asphyxia and another category for deaths with trauma but no evidence of serious antecedent asphyxia. Where there is evidence of both trauma and asphyxia without any clear evidence that one *caused* the other, we believe a clinical decision has to be made as to which factor played the dominant role in bringing about death in any given case.

Neonatal death without apparent autopsy abnormality (no histological lesion)

Such deaths were quite common in the 1958 survey. On closer examination these babies formed a rather heterogeneous (and rather unsatisfactory) group. When reanalysed in conjunction with the available clinical narrative, it is clear that most of the deaths were probably due to severe pulmonary immaturity or intrapartum asphyxia (although some very early deaths were associated with clinical evidence of respiratory distress, and these were probably deaths due to surfactant deficiency that occurred before there was time for the secondary proteinaceous exudate to manifest itself as a hyaline membrane). We suggest, therefore, that, while a category of this type should be retained, it should only be used for babies who are manifestly previable, or who have histological evidence of severe structural pulmonary immaturity (and not merely of biochemical immaturity due to surfactant deficiency), and redefined as such.

Unfortunately it can be extremely difficult to decide whether a small and very immature baby who dies within an hour or two of birth died of intrapartum asphyxia, untreatable pulmonary immaturity, or hyaline membrane disease. A comparison of coding practice between Scotland and the North of England revealed a major difference in practice here even though both surveys were using identical written criteria for classifying these deaths (Table 1). Such problems are not unimportant if the results of any analysis using this classification are to be used to audit clinical practice, since death from intrapartum asphyxia shortly after delivery might well be looked upon as being the obstetrician's 'fault', and death from hyaline membrane disease as being the paediatrician's 'fault', while death from untreatable structural lung immaturity is obviously no one's 'fault'. We have attempted to obtain some uniformity of practice in this area by classifying all these babies as dying of hyaline membrane disease if they were ever got 'into a clinically stable condition after resuscitation with adequate respiratory exchange and a good circulation'. Other babies are arbitrarily categorized as dying of intrapartum asphyxia if they were of more than 26 weeks (188 days) gestation at birth, and as dying of pulmonary immaturity if they were 26 weeks gestation or less (unless there are overwhelming grounds for interpreting the available evidence differently). Where gestation is completely unknown it may be acceptable to use a birthweight of 750 g to separate these two groups (although this does not quite equate with a gestation of 188 days).

Intraventricular haemorrhage and periventricular infarction

Intraventricular bleeding (IVH) with or without periventricular ischaemia and hyaline membrane disease (HMD) or the late sequelae of treated hyaline membrane disease often coexist.

In the 1958 survey an attempt was made to say in such cases which of these two factors was the more important and then to ascribe death to this cause. We have not found such an arrangement sustainable and believe that any clinical subclassification should contain a category for 'HMD with IVH' where *both* these factors are clearly of major relevance.

Other intracerebral haemorrhage (or infarction)

Other intracerebral bleeding serious enough to cause death is rare after cases of intraventricular haemorrhage or periventricular ischaemia or haemorrhage of the type normally associated with preterm delivery before 32 weeks gestation and cases clearly caused by intrapartum trauma or asphyxia are excluded. We have, however, almost against our better judgement, been prevailed upon to include such a category because such deaths obviously merit close examination and study. For most epidemiological purposes, such deaths are usually best grouped with other 'Miscellaneous' deaths.

Massive pulmonary haemorrhage

Much the same argument applies to cases of pulmonary haemorrhage. For reasons that are far from clear such deaths are now very much rarer than they were in 1958. It is difficult, therefore, to justify the retention of a specific subcategory for these deaths. These deaths should be identified as such but then included for most epidemiological purposes with other miscellaneous deaths due to other known, but rare, fetal and neonatal conditions.

Isoimmunization

We have retained isoimmunization as a separate category for historical reasons, but others may wish to classify such deaths with other miscellaneous deaths now isoimmunization is so uncommon, since these cases can easily be identified as such by reference to the maternal classification (Cole *et al.* 1986).

Infection

Intrapulmonary infection was separated from extrapulmonary infection in 1958. Deaths due to primary pulmonary infection are now relatively rare and we believe it is therefore better to group together all deaths where infection is the primary factor responsible for the chain of events leading up to the child's death. For clinical purposes it is probably more helpful to subclassify such cases by their timing in relation to birth rather than by the site of, or the organism responsible for, the infection. We have elected to include necrotizing enterocolitis, a condition almost unknown to the pathologists responsible for the 1958 survey, with deaths due to infection rather than with other 'specific (miscellaneous) neonatal conditions'. We do not imply by this that we think bacterial invasion of the bowel is necessarily the primary trigger factor; generalized infection does, however, frequently supervene in cases where necrotizing enterocolitis eventually leads to death.

Comment

We have tried to modify and adapt the classification used during the 1958 British Perinatal Mortality Survey in such a way that it can be applied without too much uncertainty in most cases where autopsy information is sketchy or nonexistent (without implying that the lack of any detailed autopsy information in many current perinatal deaths is anything other than a national disgrace). The changes proposed are not, however, in themselves, so radical as to invalidate any comparison with the 1958 data.

We have recommended a classification into 11 groups. However, some further subclassification is almost certainly called for. This can best be achieved in a flexible way by recording the International Classification of Disease (ICD) code number for each main factor contributing to the death, but an enlargement of the proposed classification into a total of 24 subgroups as suggested in the final two columns of Table 2 is all that is necessary for most purposes. Such a detailed subclassification is, nevertheless, unwieldy for most epidemiological purposes, unless the number of deaths available for analysis is as large as it was in the 1958 survey (6500 perinatal deaths). Even in their analysis of the 2300 deaths in March, those responsible for the 1958 study felt that the 18 subgroups they had defined were better regrouped, for most purposes, under just six major headings (Butler & Bonham 1963, p. 196 and Fig. 65.1). These six groups are, in fact, very similar to those proposed independently by Wigglesworth (1980). The 24 subcategories we have suggested here can easily be reduced to the same six major categories as outlined in Table 3.

The main requirement of any such classification, if it is to be used for epidemiological purposes, is consistency of interpretation. Experience with the continuing perinatal mortality surveys now in operation throughout Scotland and in the Northern Regional Health Authority in England shows that consistency can be hard to achieve even when definitions of the various terms in use are available to all concerned at local level (Table 1). We believe it may be helpful, in this context, to take a leaf out of the botanist's book (if the unintentional pun implicit in this phrase can be excused) and construct a hierarchical, dichotomous, decision-making tree to cope with this difficulty (see Appendix). This inevitably introduces a degree of arbitrariness but it does reduce inconsistency of classification. Thus when a baby with Trisomy 21 dies with congenital heart disease it can be difficult to decide whether to classify this death as due to the 'chromosomal defect' or to the 'congenital heart disease'. Reference to the Appendix can help to resolve many of these dilemmas.

Experience in the Northern region suggests that the use of this key greatly improves consistency of classification, although a few inconsistencies will still occur from time to time if survey returns are not scrutinized centrally. A pathology review panel scrutinizing some of the histological material (including, in particular, pulmonary histology) can further enhance consistency. The classification outlined in Table 2 is relatively unaffected by such issues, however, and the summary classification in Table 3 is almost completely unaffected as long as allocation is reached using the approach outlined above. If this is not done, however, the apparently simple classification outlined in Table 3 is capable of being interpretated in a variety of different ways. Thus it has been argued that all stillbirths due to proven placental abruption before the onset of labour should be grouped with other 'specific conditions causing death' rather than with 'unexplained death prior to the onset of labour' since the cause of the asphyxia is not unknown (even if it is still unexplained). This would move many deaths from category B to category E in Table 3. Such an approach would be logical enough but it would be radically different from the way in which this grouping was first employed in the 1958 survey. Similar uncertainty would surround decisions about whether to ascribe the death of a very immature baby shortly after birth to category C or category D, rendering even the simple grouping outlined in Table 3 almost useless for epidemiological purposes.

Table 3. A short classification of perinatal death

A *Congenital anomaly* Deaths that had their origin at conception or during embryogenesis (Categories 1–6)

B *Unexplained death prior to the onset of labour:* Deaths due to asphyxia and other unexplained antepartum deaths (Category 8)

C *Intrapartum events·* Deaths before or after birth due to events occurring during labour (Categories 9 and 10)

D *Conditions consequent upon preterm birth:* Deaths due to pulmonary immaturity, hyaline membrane disease, intraventricular and periventricular haemorrhage or infarction or their complications (Categories 11–15)

E *Other specific conditions:* All other deaths due to intracranial haemorrhage. Deaths due to isoimmunization, or infection, and deaths due to other specific miscellaneous conditions including unequivocal cot death (Categories 7 and 16–22)

F *Unclassified:* Inadequately documented deaths (Categories 23 and 24)

It may be questioned whether there is any need for an intermediate classification between the simple one shown in Table 3 and one based on the use of ICD codes as proposed by the FIGO Standing Committee on Perinatal Mortality and Morbidity (1982). We feel that such an intermediate classification does have a place in the analysis of perinatal death over a period of time and for comparative purposes in different NHS regions. Derivation of a primary pathological finding or mode of death working backward from the ICD codes is highly dependent on precise and accurate coding and this is all too seldom achieved in practice.

We do, however, stress that any interpretation of perinatal mortality depends not only on an understanding of the nature of the dead population but also on an understanding of the total birth population from which the deaths have been derived. Comparisons based on the use of this, or any other, classification of perinatal death will be uninterpretable unless factors such as the birthweight and gestational age distribution of the surviving, as well as the dead children are taken into account.

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The Co-ordinating Group responsible for the Northern Regional Survey currently consists of Dr R. G. Welch (Chairman), Mr S. L. Barron, Mr C. H. W. Bullough, Dr E. N. Hey, Mr R. Layton, Mr R. A. McNay and Dr D. Morris.

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Appendix

A flow chart for classifying fetal and neonatal factors involved in perinatal death

1. Was the baby stillborn?
   Yes .... Go to 2
   No Go to 15

2. Did the fetus have a major malformation incompatible with life (with or without surgery) or of a type associated with a significantly increased risk of intrauterine death (e.g. certain chromosome anomalies, amniotic band anomalads, etc)?
   Yes . . Go to 10
   No . Go to 3

3. Was death due to blood group incompatibility or a complication of treatment for blood group isoimmunization?
   Yes . . . . Isoimmunization (Category 7)
   No .... Go to 4

4. Did the fetus have any other recognizable cause for death such as a tumour, idiopathic hydrops fetalis or evidence of the twin-to-twin transfusion syndrome?
   Yes . Miscellaneous (Category 21)
   No . . Go to 5

5. Was there evidence of fetal infection?
   Yes . Go to 36
   No ... . Go to 6

6. Was the baby delivered by elective section before the onset of labour?
   Yes ... Antepartum asphyxia (Category 8)
   No Go to 7

7. Was the birth concealed, unattended, or completely undocumented?
Yes .. Unattended delivery (Category 23)
No .... Go to 8

8. Did the fetus die during delivery and show autopsy evidence of trauma (such as rupture of the liver, splenic avulsion, fracture/dislocation of the occipital bone, or serious damage to the falx, tentorium, great cerebral vein, or cervical spine) not probably caused by urgent attempts to deliver an already very asphyxiated baby?
Yes . Birth trauma (Category 10)
No .... Go to 9

9. Was there reasonable evidence that the baby was alive at the start of labour?
Yes . Intrapartum asphyxia (Category 9)
No ..... . Antepartum asphyxia (Category 8)

10. Did the baby have a structural chromosome abnormality?
Yes . . Chromosomal defect (Category 1)
No . Go to 11

11. Did the baby have a genetic disorder known to be carried by a single gene (eg. an inborn error of metabolism, cystic fibrosis etc)?
Yes . . .. Inborn error of metabolism (Category 2)
No .... Go to 12

12. Did the baby have a neural tube defect (ie, anencephaly, encephalocele, meningocele, or meningomyelocele, other than in association with the Meckel syndrome)? Note that isolated hydrocephalus is not generally considered to be a neural tube defect.
Yes .... Neural tube defect (Category 3)
No . . Go to 13

13. Did the baby die from congenital heart disease in the absence of any other major malformation?
Yes .. .. Congenital heart disease (Category 4)
No Go to 14

14. Did the baby die from a major abnormality of the renal tract (or from pulmonary hypoplasia as a secondary consequence of this)?
Yes . Renal abnormality (Category 5)
No . Other malformation (Category 6)

15. Did the baby have any genetic or structural defect arising at conception or during embryogenesis incompatible with life, or potentially treatable but causing death?
Yes . . .. Go to 10
No .... Go to 16

16. Was death due to blood group incompatibility or a complication of treatment for blood group isoimmunization?
Yes Isoimmunization (Category 7)
No ... Go to 17

17. Was the birth concealed, unattended, or completely undocumented?
Yes .... Unattended delivery (Category 23)
No . ... Go to 18

18. Was there evidence of rupture of the liver, splenic avulsion, fracture/dislocation of the occipital bone, or serious damage to the falx, tentorium, great cerebral vein, or cervical spine, at autopsy, and did this contribute more to the baby's eventual death than any associated antepartum or intrapartum asphyxia?
Yes .... Birth trauma (Category 10)
No .... Go to 19

19. Were there significant respiratory problems within 12 hours of birth?
    Yes . Go to 20
    No .... Go to 30

20. Was there retrospective evidence of pulmonary dysplasia or hypoplasia (eg. a lung weight of less than 60% than that predicted for the baby's birthweight)?
    Yes .... Go to 21
    No ... Go to 23

21. Was there a major renal tract anomaly?
    Yes .. Renal abnormality (Category 5)
    No Go to 22

22. Was there reasonable retrospective evidence of prolonged loss of amniotic fluid for at least one week with probable secondary oligohydramnios?
    Yes Miscellaneous (Category 21)
    No . Other malformation (Category 6)

23. Was there good retrospective evidence that the baby was infected at birth?
    Yes . Go to 36
    No . Go to 24

24. Was there evidence of severe aspiration of meconium or vernix at birth?
    Yes . Intrapartum asphyxia (Category 9)
    No .. Go to 25

25. Did it ever prove possible to get the baby into a clinically stable condition after resuscitation, with adequate respiratory exchange and a good circulation?
    Yes .... Go to 27
    No ... Go to 26

26. Was the baby less than 27 weeks gestation at birth?
    Yes .. Pulmonary immaturity (Category 11)
    No .... Intrapartum asphyxia (Category 9)

27. Was the respiratory distress complicated by severe intraventricular bleeding with blood filling the whole ventricle or by bleeding extending into the parenchyma of the brain or by periventricular infarction?
    Yes HMD with IVH (Category 13)
    No . ... Go to 28

28. Did the baby die from infection acquired while receiving ventilatory support for hyaline membrane disease?
    Yes .. HMD with infection (Category 14)
    No . Go to 29

29. Did the baby die of the respiratory distress syndrome (hyaline membrane disease) or any of its other known complications?
    Yes . . HMD (Category 12)
    No . Go to 30

30. Was there evidence that death was caused by intraventricular haemorrhage with blood filling the lateral ventricle or extending into the parenchyma of the brain or with signs of periventricular infarction?
    Yes . Intraventricular haemorrhage (Category 15)
    No .... . Go to 31

31. Did asphyxia during delivery initiate the train of events that led to the baby's death?
    Yes Intrapartum asphyxia (Category 9)
    No ..... Go to 32

32. Was there other evidence of significant intracranial bleeding or ischaemia?
Yes . .. Other intracranial bleeding (Category 16)
No Go to 33

33. Did the baby die of necrotizing enterocolitis or its secondary complications?
Yes ... ... Necrotizing enterocolitis (Category 17)
No . Go to 34

34. Did the baby die of infection or its secondary complications?
Yes Go to 35
No Go to 37

35. Was the organism that caused the infection acquired after birth?
Yes .... Postpartum infection (Category 20)
No .. . .. Go to 36

36. Did the baby become infected before the onset of labour?
Yes ..... Antepartum infection (Category 18)
No ...... Intrapartum infection (Category 19)

37. Was the death classified after full investigation as a sudden unexplained infant death (Cot death)?
Yes . Cot death (Category 22)
No .. .. Go to 38

38. Did the baby have some other recognizable cause of death?
Yes .... Miscellaneous (Category 21)
No Undocumented or unclassified (Category 24)

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Comparisons of data from regional perinatal mortality surveys

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Summary. The standard format in which NHS regions are invited to submit data from their perinatal mortality surveys for comparative analysis in the *British Journal of Obstetrics and Gynaecology* is described. Some examples of the way these data can and will be used to compare regional differences in mortality patterns are given and possible future developments are discussed. Although the term perinatal mortality is used in the title, it is hoped that surveys will cover stillbirths and neonatal deaths and also, where possible, late fetal deaths of less than 28 weeks gestation.

An editorial in this Journal last year announced that the editorial board had decided to publish a supplement on perinatal mortality in 1987 and at intervals thereafter (Chalmers 1985). The purpose of this is to bring together data from the regional surveys which are now taking place (Mutch 1986). It is hoped that this will encourage greater consensus about the framework for doing these surveys so that as well as auditing their own practice, NHS regions can make valid comparisons between patterns of fetal and neonatal mortality rates in their own and other regions.

Two papers in this issue (p. 1204 and 1213) outline methods of classifying maternal, fetal and neonatal factors. These have been developed in the course of work done over the past 2 years by Scotland and in the Northern region with the aim of improving the comparability of information.

Although a more ambitious format may be appropriate for this supplement in the future, it has been decided to make a modest start in 1987.

This paper outlines the format in which those doing regional surveys are invited to send data for deaths of babies born in 1986 and, where possible, 1984 and 1985. Data from Scotland and the Northern region are used to show some possible types of comparative analyses which might be used to compare regional data in the future. The article ends by outlining current thoughts about future developments.

Data collection and classification

It should be stressed that data from surveys are to be provided in tabular form rather than as individual records. For compatibility with other sources of national statistics the tabulated data should cover registered stillbirths (fetal deaths after 28 completed weeks gestation) and all neonatal deaths (deaths occurring <28 completed days after live birth) where possible, or if late neonatal deaths are not available for analysis, deaths occurring <7 days after live birth. It is preferable for surveys to include late neonatal deaths because of the extent to which these have their origins in the perinatal period. Ideally, late fetal deaths <28 completed weeks gestation but at least 500 g in weight or 22 weeks gestation) should also be included in surveys with other perinatally related events (Chiswick 1986). As these are not registrable stillbirths, however, it is unlikely that NHS regions will be able to provide data on these in the near future. Experience in Scotland has shown that only those hospitals that regularly include late fetal deaths under 28 weeks in their local perinatal mortality reviews

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are able to produce reliable information about numbers and classification (Information Services Division 1986).

A second important criterion is that NHS regions should be able to provide data about all deaths of babies born to women resident in their geographical area, including women delivered in other NHS regions. The Scottish data are available on a national basis, so the problem of within country cross border flow does not arise. Details of births and neonatal deaths to the resident population can be obtained from the copies of the entry in the register sent to the District Health Authority (DHA) or Health Board (HB).

Within Scotland or within England and Wales, the local Registrar sends a copy of the register entry to the Health Board or District Health Authority in which the parent registering the birth normally lives. No such transfer of information occurs across the border between Scotland and England, and births and deaths of residents occurring in the other country are counted within the statistics of that country. In England and Wales, these are included in tabulations along with other births (or deaths) to residents outside England and Wales. In Scotland such births (or deaths) are attributed to the place of occurrence. It is recommended that births and neonatal deaths to women living outside England and Wales be included with the survey data from the NHS region (or country in the case of Wales) in which they occur.

In principle, copies of birth and death registrations are sent to District Medical Officers. Since the Griffiths reorganization, however, some districts do not have District Medical Officers or other community physicians. It would be good practice, therefore, if those responsible for co-ordinating regional surveys identified the person in each district to whom registration details are sent and arranged to receive copies of those which pertain to stillbirths and neonatal deaths. At the same time, it is important to liaise not only with community physicians, but also information officers and other relevant staff of DHAs and RHAs.

In England and Wales a second opportunity to obtain data occurs after the Office of Population Censuses and Surveys (OPCS) sends to Regional Health Authorities (RHAs) and the Welsh Office computer tapes containing coded information about the previous year's births and deaths of people living in their area. This information is derived from the 'draft entries' sent to OPCS by Local Registrars. In addition to the details provided by the person registering the birth, the Registrars obtain information about birthweight from the DHA. This is derived from birth notifications. Because it is considered to be clinical information, Registrars are not instructed to ask parents for birthweights.

Of course, even in the Thames regions, a high proportion of women are delivered in the region in which they live and any resulting stillbirths and neonatal deaths will be known to local clinicians without waiting for registration details. Cross checks are still useful, however, for monitoring the completeness and accuracy of both survey and registration data.

It should be noted that while a study in Northern Ireland identified considerable underregistration, particularly of stillbirths (Scott *et al.* 1981), this is not the case in the rest of the United Kingdom. Cross checks between registration data and survey data in the Northern and North East Thames regions found very little incompatibility.

In order to be able to derive the tables specified later, NHS regions should ensure that the following data items are recorded locally for each stillbirth and neonatal death.

(1) Cause of death classified by maternal factors as described by Cole *et al.* in this issue (p. 1204).
(2) Cause of death classified by fetal and neonatal factors as described by Hey *et al.* in this issue (p. 1213).
(3) Multiplicity, in order to be able to analyse singleton and multiple births separately. It would be useful, for local purposes, to distinguish between twins, triplets, quadruplets, quintuplets and sextuplets, but these details are not needed for regional comparisons.
(4) Birthweight in grams. The article by Chiswick in this issue (p. 1236) stresses that this should be the initial measurement made after birth, to the nearest gram, preferably on an electronic weighing balance.
(5) Timing of death. This should be subdivided into: late fetal death after at least 22 weeks but under 28 weeks gestation (if possible), antepartum stillbirths, intrapartum stillbirths, deaths occurring <7 completed days after live births and deaths occuring from 7 to 27 days after live birth.

This is not, of course, an exhaustive list of data which could be collected within NHS regions in perinatal surveys. Data items which would be recorded for local use include district of residence, place of delivery and socio-economic information about parents.

Regional tabulations

Regions are invited to submit three tabulations, containing numbers of fetal and neonatal deaths.

(1) *Maternal factors by birthweight.* Birthweight should be in 250 g groups under 1500 g (<500 g, 500–749 g, 750–999 g, 1000–1249 g and 1250–1499 g) and in 500 g groups from 1500 g on (1500–1999 g, 2000–2499 g, 2500–2999 g, 3000–3499 g, 3500–3999 g, 4000–4499 g, ≥4500 g). Births with unknown birthweight should be identified separately. The tabulation should be done for singleton and multiple births separately, showing age at death. An example of part of the layout for the tabulated data is shown in Fig. 1.

(2) *Fetal and neonatal factors by birthweight.* The data should be tabulated as above, showing age at death and singleton and multiple births separately.

(3) *Maternal factors by fetal and neonatal factors.* The data are tabulated to show singleton and multiple births separately and time of death.

These tables are, of course, too detailed to be of interest as they stand but the reason for asking for more detailed data is the need for sufficient flexibility in analysing and combining the data and calculating rates as has been done in Tables 1–5. If NHS regions wish to participate in this, it would be almost essential that a regional contact is appointed to facilitate the exchange of information, particularly about women who are delivered outside their home NHS region. Such a contact might also wish to receive copies of the layout for the proposed tabulations above, in order to clarify the way data should be submitted, either on paper or in computer readable form.

In this article, mortality rates for the Northern region have been calculated by dividing the numbers of fetal and neonatal deaths by the relevant numbers of births to residents of the Northern region. These were derived from OPCS data. NHS regions who want to do this for their own data can produce the relevant tabulations using the computer tapes of birth data provided to the RHA annually by OPCS. It will be necessary to tabulate the numbers of singleton and multiple live and stillbirths separately by birthweight. Those who are unable to do so may be able to request data from the OPCS unpublished reference tabulations. OPCS will, however, have to make a charge to cover the clerical costs of extracting the data required from more detailed tabulations.

In addition, from 1986 onwards, OPCS will include birthweight distributions for each district on its VS2 tabulations. These will supersede the SD52 tabulations which are currently circulated to RHAs and DHAs. Our understanding is that these will not be subdivided into singleton and multiple births and that they will use 500 g groupings throughout. OPCS has been informed of the interest among obstetricians and paediatrians in using 250 g groupings below 1500 g and subdivisions into singleton and multiple births, but discussions have yet to take place about whether it would be feasible to publish them routinely and, if so, what level of aggregation would be appropriate. Even for singletons such data would be of limited use at district level for single years because of the small numbers involved. For singleton births it might therefore be more appropriate to ask for regional data for single years and district data aggregated over 3-year periods, while broader

	Birthweight Under 500 g		500–749 g . . . etc	
	Single	Multiple	Single	Multiple
Congenital anomaly				
Late fetal deaths under 28 weeks				
Antepartum stillbirths				
Intrapartum stillbirths				
Early neonatal deaths				
Late neonatal deaths				
etc. with totals at bottom of table				

Fig. 1. The top left-hand corner of the tabulation recording maternal factors by birthweight.

Table 1. Comparison of crude stillbirth and neonatal mortality rates, Scotland and Northern region 1985

	Singleton				Multiple				Total			
	Scotland		Northern region		Scotland		Northern region		Scotland		Northern region	
	No	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No	Rate
Antepartum stillbirths	275	4·19	165	4·11	18	12·94	21	23·76	293	4·37	186	4·52
Intrapartum stillbirths	59	0·90	42	1·04	10	7.19	3	3.39	69	1.03	45	1·10
Early neonatal deaths	250	3·83	157	3·92	41	30·08	21	24·42	291	4·36	176	4·58
Late neonatal deaths	65	0·99	38	0·95	8	5·87	6	6·98	73	1·10	44	1·08
Live births	65 308		40 018		1363		860		66 671		40 878	

Stillbirths are expressed as the rate per 1000 total births and neonatal deaths as the rate per 1000 live births

aggregation will be needed for analysing multiple births.

In Scotland, clinical data have been available on over 98% of births since 1976 (Cole 1980). Birthweight distributions are calculated by applying the percentage distributions from the SMR2 form to the numbers of registered live and stillbirths.

It may seem strange that no tabulations by gestational age have been proposed. This is because this information is not recorded when live births are registered in England and Wales and, therefore, no denominators are available. These data were collected for a 10% sample of births through the Maternity Hospital In-Patient Enquiry, but this data collection system ceased at the end of 1985. In Scotland the data are collected through the SMR2 system and are available as both a 'best clinical estimate of gestation' and as a calculated gestational age derived by subtracting the date of last menstrual period from the date of delivery.

How the data can be used

In what follows, examples are given of how the data submitted in the three tabulations described above could be analysed and aggregated to enable comparisons to be made between NHS regions. The analysis is by no means exhaustive, so what is eventually published in 1987 may differ from what is given here.

Table 2. Stillbirth, perinatal mortality and neonatal mortality rates, Scotland and Northern region 1985

	Birthweight (g)					
	<1000		≥1000		Total	
	Scotland	Northern region	Scotland	Northern region	Scotland	Northern region
Stillbirths/1000 total births						
Congenital anomaly	19·5	32·7	0·4	0·3	0·5	0·5
Other causes	239 0	235·3	4·2	4·3	5·0	5·2
All causes	258·5	268·0	4·7	4·6	5·4	5.6
Perinatal deaths/1000 total births						
Congenital anomaly	29·3	58·8	1·7	1·5	1·8	1·8
Other causes	692·7	666·7	5·8	5·8	8·0	8·2
All causes	722·0	725·5	7·6	7·3	9·8	10 0
Neonatal deaths/1000 live births						
Congenital anomaly	13·2	25·0	1·7	3·7	1·7	1·7
Other causes	717·1	641·7	2·1	1·8	3·7	3·7
All causes	730·3	666·7	3·8	3·5	5·4	5·4

Table 3. Stillbirth and neonatal death rates by maternal factors and fetal and neonatal factors, singletons only, Scotland and Northern region 1985

	Fetal and neonatal factors									
	Congenital anomaly		Asphyxia and trauma		Pulmonary immaturity and hyaline membrane disease		Other and not known†		Total	
Maternal factors	Scotland	Northern region	Scotland	Nothern region	Scotland	Northern region	Scotland	Northern region	Scotland	Northern region
Stillbirths/1000 total births										
Congenital anomaly	0·46	0·45							0·46	0·45
Pre-eclampsia			0·47	0·40					0·47	0·40
Antepartum haemorrhage			0·99	1·00					0·99	1·00
Other and not known*			0·40	0·32			0·21	0·12	0·61	0·45
Unexplained			2·56	2·84				0·02	2·56	2·86
Total	0·46	0·45	4·42	4·55			0·21	0·15	5·09	5·15
Neonatal deaths/1000 live births										
Congenital anomaly	1·67	1·70							1·67	1·70
Pre-eclampsia			0·03		0·18	0·08	0·03	0·03	0·24	0·10
Antepartum haemorrhage			0·21	0·25	0·28	0·28	0·05	0·10	0·54	0·62
Other and not known*			0·15	0·18	0·08	0·10	0·52	0·58	0·75	0·85
Unexplained			0·48	0·32	0·80	1·03	0·35	0·25	1·62	1·60
Total	1·67	1·70	0·87	0·75	1·33	1·47	0·95	0·95	4·82	4·88

* Includes: Isoimmunization; Mechanical; Maternal disorder; Miscellaneous; Unclassifiable; No information.

† Includes: Isoimmunization; Intracranial haemorrhage; Infection; Miscellaneous; Unclassified or unknown.

Table 4. Stillbirths and neonatal deaths by maternal factors and fetal and neonatal factors, multiple births only, Scotland and Northern region 1985

	Scotland		Northern region	
	No.	Rate/1000 total births	No	Rate/1000 total births
Maternal factors				
Congenital anomaly	10	7·19	3	3·41
Pre-eclampsia	3	2·16	5	5·68
Antepartum haemorrhage	3	2·16	1	1·14
Other and not known*	6	4·31	9	10·23
Unexplained	55	39·54	33	37·50
Total	77	55·36	51	57·96
Fetal and neonatal factors				
Congenital anomaly	10	7·19	3	3·42
Asphyxia and trauma	27	19·41	23	26·14
Pulmonary immaturity and hyaline membrane disease	34	24·44	16	18·18
Other and not known†	6	4·31	9	10·23
Total	77	55·36	51	57·96

* Footnote as Table 3.
† Footnote as Table 3

Table 1 shows crude mortality rates for Scotland and the Northern region, with stillbirths subdivided into antepartum and intrapartum deaths. Before 1986 when the new stillbirth certificate was introduced, this distinction was not made in registration data for England and Wales. For singleton births, rates for England and Scotland are very similar while larger differences are seen in rates for the small numbers of multiple births.

In rates for the Northern region in these and subsequent tables, there are slight discrepancies between numerators derived from the Northern region's survey and denominators based on OPCS birth statistics. The Northern region's survey is based on deaths of babies born in 1985. The OPCS birth file mainly consists of details of births which occurred in 1985, but also includes those which occurred in 1984 which were registered after January 1985 and excludes 1985 births registered after January 1986. Similar principles apply to birth data for other years.

Table 5. Estimated death rates in 250-g groups, Scotland and Northern region 1985

	Total stillbirths and neonatal deaths			
	Scotland		Northen region	
Birthweight (g)	No.	Rate*	No.	Rate*
<500	14	1000	13	1000
500–749	66	1000	39	696
750–999	84	667	60	682
1000–1249	76	352	25	253
1250–1499	56	210	41	151

*Per 1000 total births.

Most of the OPCS published mortality statistics are derived from death files based on the year of registration. In addition, OPCS produces ‘birth cohort infant mortality linked files’ based on the year of birth, but this happens some time after its basic data files are compiled. This is because many postneonatal deaths take place in the calendar year after the baby was born. In Scotland, it has been decided to base the perinatal mortality survey on the year in which stillbirths and neonatal deaths are registered, to ensure consistency, and it is suggested that English regions may choose to do likewise, treating January birth registrations in the way described above.

In Table 2, all births and deaths are tabulated so that babies weighing under 1000 g and those whose cause of death was attributed to congenital anomaly are shown separately. Death rates attributed to congenital anomaly among babies

Table 6. Perinatal mortality rates by birthweight and country and Regional Health Authority of usual residence of mother, England and Wales 1984, Scotland 1983

Area of usual residence of mother	Total	Birthweight (g) <1500	1500–2499	≥2500	Not stated
England	10·0	363·2	44·7	3·5	238·9
Regional Health Authorities					
Northern	11·0	396·5	42·5	4·3	326·1
Yorkshire	11·6	383·3	55·3	3·9	333·3
Trent	9·7	334·5	50·0	3·2	310·3
East Anglia	8·9	327·0	46·0	3·6	133·3
North West Thames	9·0	311·1	35·8	3·2	206·3
North East Thames	9·7	320·4	43·4	3·5	175·8
South East Thames	10·5	358·4	43·3	3·5	201·7
South West Thames	8·5	342·0	42·8	3·2	333·3
Wessex	8·6	360·5	39·8	3·2	371·4
Oxford	8·7	336·5	46·6	2·6	131·1
South Western	9·3	333·3	53·5	3·5	234·0
West Midlands	12·3	446·0	46·0	3·9	218·3
Mersey	9·0	372·2	35·3	3·0	319·1
North Western	10·3	376·4	40·9	3·3	290·3
Wales	10·5	405·0	50·8	3·8	279·4
Scotland	10·7	421·5	46·8	3·7	226·2

Source: OPCS Mortality statistics (England and Wales) available in *Hansard* 10/6/86, cols 106 and 149 (w).
SMR2 (Scotland) available in *Hansard* 10/6/86 Col 113 (w).

weighing under 1000 g were lower in Scotland than the Northern region. It may be that the screening policy in Scotland is more effective in detecting malformations leading to fetal death or preterm labour in this weight group, or may also reflect differences in incidence. Otherwise, however, the stillbirth and death rates were very similar.

A fuller use is made of the classification in Table 3 in which stillbirths and neonatal deaths among singleton births are tabulated by maternal and by fetal and neonatal factors. Stillbirth rates in Scotland and the Northern region are very similar and show consistent use of the two classifications. Amongst neonatal deaths the Northern region apparently had a higher mortality attributed to hyaline membrane disease and immaturity while Scotland had higher rates for asphyxia and trauma. It is likely that this difference, which also affected the rates for multiple births shown in Table 4, arises from problems in definition which, it is hoped, can be resolved by use of the flow chart described by Hey *et al.* in this issue (p. 1213).

Multiple births are too few in number for it to be worth using the two-way classification on a regional level, so in Table 4 stillbirths and neonatal deaths combined are tabulated according to each classification separately. Although the overall rates are very similar, it is not surprising, given the small numbers involved, that there are larger differences in cause specific rates.

Death rates among babies born weighing less than 1500 g in Scotland and the Northern region are shown in Table 5. These have been tabulated in the 250 g groups recommended earlier. The Scottish data should be interpreted with caution as they were calculated using denominators derived from an estimated birthweight distribution based on 1984 data. It is thought that a very small number of babies in the 500–749 g group born in Scotland did, in fact, survive. They do illustrate, however, the marked differences in mortality within the 500 g groups under 1500 g.

Although confidence intervals have not been shown for Tables 1–5, it should be borne in mind that many of the rates are based on small numbers of events. For some analyses, it would be preferable to combine several years' data where they are available. Readers' comments on the usefulness or otherwise of this selection of tables and suggestions for further tabulations would be very welcome in planning the analyses which it is intended to publish next year.

Future developments in England and Wales

Gestational age is one of the items specified by the Steering Group on Health Services Information for collection in England from 1 April 1988 onwards. The data will be collected through District Maternity Systems, aggregated regionally and then submitted to OPCS for analysis nationally as part of the Hospital Episode System (HES). The Welsh Office plans to set up a similar system once Patient Administration Systems have been installed in each district.

When the Maternity HES system and its Welsh counterpart are under way it will be possible to use them to produce gestational age distributions for geographically defined populations, while local systems produce similar data by district of treatment. The same considerations apply to data about women's actual parity. At birth registration, only married women are asked about parity and the information collected is confined to previous births by her current or any other husband.

Meanwhile developments have taken place in the civil registration system. Birthweight is now recorded for most births registered in England and Wales. It was missing for only 0·13% of live births and 1·65% of stillbirths registered in 1985 (OPCS 1986*a*). It is essential that the relevant staff make efforts to reduce these percentages to zero by ensuring that all babies are weighed (Wilkinson & Howat 1980) and all birthweights are recorded on birth notifications so that they can be passed to OPCS, and also that birthweights are on all stillbirth certificates. Meanwhile, using existing data, the OPCS is able to provide denominators for tables specified here and use its infant mortality linked files to produce birthweight specific mortality rates.

One example of what is possible is shown in Table 6, which gives perinatal mortality in broad birthweight groups in each NHS region. It is, of course, possible to use smaller subdivisions. OPCS also subdivides tabulations by other items collected at birth registration, including multiplicity, parents' ages, mother's country of birth, father's social class, registered cause of death and place of delivery (OPCS 1986*b*).

The new forms introduced in 1986 for certifying stillbirths and neonatal deaths in England and Wales ask certifiers to identify separately maternal, fetal and other conditions leading to death. It may, therefore, be possible to use these attributed conditions to derive approximately the same categories of maternal factors and fetal and neonatal factors described in this issue of the Journal. This may eventually enable those NHS regions who do not conduct their own perinatal mortality surveys to contribute data. It would also mean that the classifications can be used in conjunction with the data which OPCS collects from parents at birth registration.

This will be of little value unless those certifying stillbirths and neonatal deaths improve the quality of the clinical information on the two certificates and update it by ensuring that revised information, including that from post mortems, is forwarded to OPCS. It is also hoped that the insights gained from using the classification described in this issue of the Journal will help in the provision of better data on death certificates.

Up to the present, the clinical information given on many stillbirth and death certificates has been unreliable and innacurate. When information recorded in case notes was compared with that recorded when certifying stillbirths during 1973 and 1977 in eight maternity units in the North West Thames region, many discrepancies were found (Edouard 1982). A study of stillbirths and neonatal deaths in the North East Thames region in 1983 (Duley 1986) reported in this issue (p. 1233) shows that this situation has not changed. An analysis of mortality among multiple births in England and Wales since 1975 (B. Botting, I. Macdonald Davies & A. J. Macfarlane, unpublished observations) found that a disturbingly high proportion of deaths was attributed simply to 'multiple pregnancy' rather than to any specific condition.

In an article describing the pilot study of the new forms of stillbirth and neonatal death certificates (Gedalla & Alderson 1984) the OPCS mentioned the suggestion that the introduction of the new certificates would be accompanied by an increase in the numbers of 'medical enquiries' addressed to the consultant responsible for the mother or the baby. This would ensure that fuller information from post mortems and perinatal meetings reached the OPCS in these instances.

It should be noted that when the OPCS receives such information, it amends its computer records but not its paper records, such as those sent to health authorities. NHS regions who wish to compare the clinical information on OPCS records with the relevant case notes should, therefore, use the annual computer tapes rather than the copies of death registrations sent to DHAs. Such comparisons would be useful in auditing the quality both of data sent to the OPCS and the NHS region's own survey data.

In Scotland, the Scottish Perinatal Mortality Survey has now become part of the country's system of routine data collection, and compares stillbirths and neonatal deaths with information collected about all births. The question therefore arises as to whether this principle could be extended to NHS regions of England and to Wales.

Some surveys carried out in England have only collected information about deaths while others have used controls. Selecting controls is not easy, yet without them there are dangers in drawing unsubstantiated conclusions about 'avoidable' factors. On the other hand, Chalmers (1984) has suggested that when what is now called the Maternity HES System is fully working, it would enable comparisons to be made with the whole population, thus making the question of controls redundant.

To enable this to happen it would be necessary to link data from HES and from the parallel system in Wales with data collected at birth registration and hence with the OPCS infant mortality linked files. The question of the HES linkage has been raised, but to our knowledge a decision has yet to be taken about it. We are not aware of whether discussions have taken place about the Welsh system. Because of cross boundary flows between England and Wales some co-ordination would be highly desirable. In any case, the timing of any further developments depends on financial resources and on how soon the Maternity HES System is working fully and smoothly.

It is, however, worth raising these questions now in order to discourage long-term duplication of effort and to encourage discussions about future developments. These discussions should involve not only those doing perinatal surveys, but also statisticians at OPCS and DHSS and information officers and community physicians in NHS districts and regions.

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A validation of underlying cause of death, as recorded by clinicians on stillbirth and neonatal death certificates

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Summary. Clinical case notes and necropsy reports were used to validate underlying causes of death as recorded and coded on 590 stillbirth and neonatal death certificates. There were 55 cases ascribed to respiratory distress syndrome, in 45 this was validated, three cases were not assigned to respiratory distress syndrome which should have been. In 102 cases death was ascribed to congenital malformation, this was validated in 96, 13 cases should have been assigned to congenital malformation, but were not. Use of available clinical and necropsy information when completing death certificates would have decreased the number of deaths attributed to respiratory distress syndrome by 13%, and increased the number certified as dying from congenital malformation by 10%.

Perinatal mortality rates are widely used in the Western World as a measure of maternity care. Enquiry into perinatal death is often advocated as an effective method of identifying how further reductions in fetal and infant mortality rates might be achieved (Chalmers 1985; Editorial 1983). Mortality data are generally more reliable than those for morbidity, particularly in the perinatal period which still lacks well-defined criteria for assessment of morbidity.

Much of the value of mortality data depends on accurate diagnosis of cause of death, which is best achieved by combining clinical data with necropsy findings. The importance of validation of causes of death as recorded on stillbirth certificates has already been emphasized (Edouard 1982). This study is an attempt to validate two major causes of death as recorded on stillbirth and neonatal death certificates by the use of necropsy reports and clinical data obtained from a structured questionnaire.

Method

A survey was carried out in the North East Thames Regional Health Authority (NETRHA) of all stillbirths and neonatal deaths occurring during 1983, the main results of which have been reported elsewhere (North East Thames Perinatal Review Group 1985). Ascertainment was by receipt of copies of draft entries stillbirth and death certificates of babies aged ≤4 weeks. These were obtained through the assistance of the Office of Population Censuses and Surveys (OPCS). The study population included deaths that occurred in the North East Thames region maternity units to residents of other NHS regions, as well as all deaths to residents of the Region. The only exclusions from the survey were deaths to non-residents occurring in the postgraduate paediatric hospitals (Queen Elizabeth Hospital, Hackney and the Hospital for Sick Children, Great Ormond Street).

Wherever possible the author checked maternity records for the units of NETRHA, and it seemed that ascertainment of deaths occurring in the North East Thames region was virtually complete. Deaths to regional residents occurring outside NETRHA could not be checked, but this is unlikely to affect the conclusions significantly as the number was small (18 cases).

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Table 1. Correlation between OPCS coding, necropsy results and clinically reported condition for mentions of respiratory distress syndrome (RDS)*

OPCS coding	Necropsy findings			
	RDS	Not RDS	No necropsy	All
ICD 769	21(12)	10(10)	24	55(22)
Clinically RDS	20(12)	7(7)	16	43(19)
RDS not mentioned clinically	1(0)	3(3)	8	12(3)
ICD other than 769	3(1)	0	0	3(1)
Clinically RDS	2(0)	0	0	2(0)
RDS not mentioned clinically	1(1)	0	0	1(1)

* Number with histology reports is shown in brackets.

The copies of the draft entries stillbirth and death certificates contained the International Classification of Diseases (ICD) code for the underlying cause of death (WHO 1978) derived by OPCS clerks from the causes of death mentioned on the certificates using the rules in the ICD code. For each death a standard clinico-pathological questionnaire was issued, which asked for the clinician's opinion as to the cause of death, whether or not a post-mortem examination, with or without histology, had been carried out, whether a congenital malformation had been present, and for details of the clinical course. The questionnaires were completed by the clinicians involved or by the author using information from the case notes. Information was obtained in 95% of cases, though this was not always complete.

Results

A total of 590 death certificates was received, 295 stillbirths and 295 neonatal deaths. Two major groups of underlying cause of death were selected for validation, respiratory distress syndrome (RDS) and congenital malformation (CM). These represented almost 30% of the deaths according to the codings allocated by OPCS using the ICD.

Respiratory distress syndrome

The correlations between different mentions of this syndrome are shown in Table 1; 55 cases were coded to ICD 769 (RDS) of which only 31 had had a necropsy. In 10 of the 31, all with histology reports, the pathological cause of death was other than RDS. These were—infection (3 cases), asphyxia (2 cases), hypoplastic lungs (2 cases), intraventricular haemorrhage (2 cases), extreme prematurity i.e. birthweight <1000 g or gestation less than 28 weeks (1 case). In 43 of the 55 (78%) there was clinical mention of RDS, but in 12 there was no such mention. In one of these, necropsy revealed evidence of RDS, but in three, all with histology, necropsy revealed no such evidence. Conversely there were three cases, with the underlying causes of death coded as intraventricular haemorrhage, prematurity (unspecified), and atelectasis of unspecified aetiology, in which necropsy revealed evidence of RDS, for two of them there was clinical evidence to support the diagnosis. Excluding the 10 cases in which necropsy had not confirmed RDS, and adding the three cases which necropsy results suggest should have been coded as RDS, would reduce the overall number in which this was probably the cause of death by 13%.

Congenital malformations

The correlations between different mentions of malformations are shown in Table 2. Congenital malformations (ICD 740–759.9) was coded as the underlying cause of death in 102 instances. Of these 69 had received a necropsy, and in 66 the pathological cause of death was also a congenital malformation. In the remaining three the pathological causes were volvulus, sudden death and extreme prematurity There were 33 deaths coded to ICD 740–759.9 which had not received a necropsy, in 31 of which there had been a clinical mention of congenital malformation, but in two there had been no such mention, apart from the entries on the death certificates men-

Table 2. Correlation between OPCS coding, necropsy results and clinically reported condition for mentions of congenital malformations (CM)

OPCS coding	Necropsy findings			
	Lethal congenital malformation	No lethal congenital malformation	No necropsy	All
ICD 740-759 9	66	3	33	102
Clinical mention of CM	64	1	31	96
No clinical mention of CM	2	2	2	6
ICD other than 740-759.9	13	0	0	13
Clinical mention of CM	13	0	0	13
No clinical mention of CM	0	0	0	0

tioning ventricular septal defect and hypoplastic lungs. Conversely there were 13 cases in which necropsy had revealed a lethal congenital malformation but the underlying cause coded was—unknown (3 cases), intraventricular haemorrhage (2 cases), intrapartum asphyxia (2 cases), respiratory distress syndrome (2 cases), extreme prematurity (1 case), intrapartum haemorrhage (1 case), cardiac arrest (1 case), pneumonia (1 case). Adjusting for these cases would increase the proportion of all deaths which were probably due to a congenital defect by about 10%.

Discussion

It is always difficult to assign with certainty a cause of death, particularly when clinical and necropsy evidence do not agree, but it seems that examination by necropsy will substantially contribute to the number of deaths attributed to congenital malformation, and subtract from those certified as dying from RDS. It follows that an increase in necropsy rate and attention to such findings when completing or updating death certification will considerably improve the quality of information on perinatal deaths.

These results should be borne in mind when comparing causes of death from different units, and when using data derived from death certification. The value of enquiry into perinatal death based on data from death certification has been clearly demonstrated (Alberman 1985). The results of this study indicate that such work is undermined by the poor quality of information on causes of death provided by clinicians.

New stillbirth and infant death certificates were introduced in January 1986, and as has already been pointed out 'this represents an unprecedented opportunity for us to put our house in order' (Chalmers 1985). It is the responsibility of every clinician involved in the completion of these certificates to ensure this opportunity is not missed.

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Commentary on current World Health Organization definitions used in perinatal statistics

A document prepared by Dr M. L. Chiswick MD FRCP DCH on behalf of the Standing Joint Committee of the British Paediatric Association and the Royal College of Obstetricians and Gynaecologists

There is an urgent need for those collecting and disseminating perinatal statistics, whether at national, regional, district, or local hospital level to adhere to standard definitions. It is strongly recommended that current World Health Organization (WHO) definitions are used in the collection of statistical data. Listed below are the relevant definitions together with short commentaries where this is felt appropriate.

It is appreciated that gestational age often cannot be determined by reference to the last menstrual period. Nonetheless, whichever method of gestational age assessment is used the definitions of various gestational categories are still appropriate. The definitions also highlight the need for all live births and fetal deaths to be accurately weighed as soon as possible after birth. Indeed, the accurate weighing of babies at birth is a necessary part of good clinical practice.

Finally, it must be stressed that adherence to the WHO definitions is for statistical purposes only and that the existing definitions governing, for example, legal requirements to register stillbirths remain unchanged.

Definitions and recommendations

Live birth

'Live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live born.'

Fetal death

'Fetal death is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles.'

Comment. The designation of extremely premature babies as 'live births' or 'fetal deaths' is influenced by whether resuscitation is attempted and whether signs of life are actively sought.

Birthweight

'The first weight of the fetus or newborn obtained after birth. This weight should be measured preferably within the first hour of life before significant postnatal weight loss has occurred.'

Comment. Ideally the naked baby, alive or dead, should be weighed to the nearest gram, if possible on an electronic weighing balance. Suitable weighing machines should be stationed in delivery units close to resuscitation trolleys so that even ill babies can be rapidly weighed at a convenient time before they are attached to apparatus that may not be relinquished for days or weeks. The initial record of weight must be the one that is recorded on all birthweight documentation, i.e. hospital birth book, special care baby unit (SCBU) notes, maternity ward notes, discharge letters, etc. It is essential to ensure that several different measurements of 'birthweight' made on the delivery unit, SCBU etc are not simultaneously used.

Low birthweight

'Less than 2500 g (up to, and including, 2499 g).'

Gestational age

'The duration of gestation is measured from the first day of the last normal menstrual period. Gestational age is expressed in completed days or completed weeks (e.g. events occurring 280 to 286 days after the onset of the last normal menstrual period are considered to have occurred at 40 weeks gestation). Measurements of fetal growth, as they represent continuous variables, are expressed in relation to a specific week of gestational age (e.g. the mean birthweight for 40 weeks is that obtained at 280–286 days gestation on a weight-for-gestational age curve).'

Comment. However gestational age is measured, a completed week is 7 days. Thus a pregnancy at 40 weeks (280 days) on 26th July is only 39 weeks (279 days) on 25th July; and not 41 weeks (287 days) until 2nd August.

Preterm

'Less than 37 completed weeks.'

Comment. A birth is preterm if it occurs up to and including the 258th day of gestation. A new day commences at midnight. Thus a pregnancy at 37 weeks (259 days) on 4th July is classified as preterm if the baby is born on 3rd July at 23.39 hours.

Term

'From 37 to less than 42 completed weeks.'

Comment. Counted as 259 days up to and including 293 days.

Post-term

'Forty-two completed weeks or more.'

Comment. Counted as 294 completed days or more.

Perinatal mortality statistics

'It is recommended that national perinatal statistics should include all fetuses and infants delivered weighing at least 500 g or, when birthweight is unavailable the corresponding gestational age (22 weeks) or body length (25 cm crown-heel), whether alive or dead. It is recognized that legal requirements in many countries may set different criteria for registration purposes, but it is hoped that countries will arrange the registration or reporting procedures in such a way that the events required for inclusion in the statistics can be identified easily. It is further recommended that less mature fetuses and infants should be excluded from perinatal statistics unless there are legal or other valid reasons to the contrary.'

Comment

In Britain, the 'fetal death' component of perinatal mortality includes only those fetuses who have completed 28 weeks (196 days) in the womb. This is convenient only because it corresponds with the legal requirement to register stillbirths who have, by definition, completed 28 weeks (196 days) in the womb. Thus, a fetus that is 28 weeks (196 days) on 1st May is not classified as stillborn if born dead on 30th April at 23.59 hours but is classified as an abortion. However, this restrictive interpretation of perinatal mortality (PNM) is unsatisfactory for many reasons, not the least being that it is illogical to include within the liveborn component of PNM *all* babies regardless of their gestational age.

Thus there is much sense in defining PNM as 'fetal deaths weighing 500 g or more *PLUS* deaths occurring less than 7 completed days after birth (i.e. 6 d 23 h 59 min or less) in babies weighing 500 g or more'. The inclusion of extremely low birthweight babies within the definition of PNM underlines the need for all fetal deaths and live births to be accurately weighed. In this way PNM can be analysed within specific birthweight groups (see below) and when comparing PNM rate, allowances can be made for differences in birthweight distributions between populations.

Statistical tables

'The degree of detail in cross-classification by cause, sex, age, and area of territory will depend partly on the purpose and range of the statistics and partly on the practical limits as regards the size of particular tables. The following patterns, designed to promote international comparability, consist of standard ways of expressing various characteristics. Where a different classification is used (e.g. in age-grouping) in published tables, it should be so arranged as to be reducible to one of the recommended groupings.'

(a) *Age classification for special statistics of infant mortality*

(i) Under 24 h, 1–6 days, 7–27 days, 28 days up to but not including 3 months, 3–5 months, 6 months but under 1 year.
(ii) Under 7 days, 7–27 days, 28 days but under 1 year.

Comment

Early neonatal death (included in PNM): death less than 7 completed days from birth (i.e. up to and including 6 d 23 h 59 min). May be further subdivided as follows: under 1 h, 1–23 h, 24–167 h.

Late neonatal death (not included in PNM): death from 7 completed days to less than 28 days from birth (i.e. up to and including 27 d 23 h 59 min).

Post neonatal death: death from 28 completed days to less and 1 year from birth (i.e. up to and including 364 days).

(b) *Birthweight classification for PNM statistics*

By weight intervals of 500 g, i.e. 500–999 g, 1000–1499 g, 1500–1999 g etc.

(c) *Gestational age classification for PNM statistics*

Under 28 weeks (under 196 days), 28–31 weeks (196–223 days), 32–36 weeks (224–258 days), 37–41 weeks (259–293 days), 42 weeks and over (294 days and over).

Comment. The influence of birthweight and gestational age on mortality is particularly marked in very-low-birthweight babies. Therefore data should be collected in a way that allows birthweight groupings to be expressed also by intervals of 250 g (e.g. less than 500 g, 500–724 g, 725–999 g, 1000–1249 g etc.) and by ungrouped gestational ages.

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Assessment of an on-line computerized perinatal data collection and information system

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Summary. An on-line maternity data collection system has been designed to provide the information required for perinatal audit and to allow many of the letters and forms required for effective communication in pregnancy to be produced automatically. The system meets the requirements of the Korner Committee on Health Services Information and has been approved by the Computer Policy Committee. Pregnancy is followed prospectively from the first antenatal clinic visit until the file is closed 28 days after delivery. Data are entered by midwives and secretaries onto a network of microcomputers placed at convenient points in the maternity unit. The system has been fully operational with no significant problems since the beginning of 1984 and has led to improved communication between hospital and the community. Analysis of 253 consecutive case notes showed a high level of accuracy of the data recorded on computer. Reports and clinical audit are readily available both from the system locally, from standard programmes on the regional mainframe computer and via a mainframe computer at London University

Obstetricians are used to auditing their work, a good example being the triennial Maternal Mortality Report, but manual systems involve time-consuming sorting of data which is often inaccurate. With the advent of the micro- and minicomputer, a number of groups have reported such applications as on-line data collection, immediate production of reports and audit (Maresh *et al.* 1982; Saunders *et al.* 1982; Houlton *et al.* 1984). After our initial experience with a Commodore PET microcomputer (Maresh *et al.* 1983), we have been collaborating closely with the North West Thames Regional Health Authority in the design of a system which would meet both regional and local clinical requirements, and take into account the recommendations of the National Perinatal Epidemiology Unit (Mutch & Elbourne 1983). In addition, we have taken advantage of the rapid improvements in microcomputer systems.

Coincident with our work, the Steering Group on Health Services Information (1981) (the Korner Committee) were drafting their maternity report and we were given a grant by them to purchase new computer equipment to pilot their recommendations. Their final maternity proposals (Steering Group on Health Services Information 1985), made in collaboration with representatives from the Royal College of Obstetricians and Gynaecologists and the British Paediatric Association, have a large 'minimum data set' which is designed to provide enough information for clinical audit and effec-

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tive service planning. Regional health authorities agreed to implement these final recommendations by 1988. A recent report by the Computer Policy Committee (1985) assesses the systems being used in the six units that were piloting the Korner Committee proposals.

This paper describes the system developed in the Department of Obstetrics and Gynaecology at St Mary's Hospital, London, includes an analysis of the first 2 years of full operation and makes proposals for the future.

Methods

Registration of women at the booking clinic began in October 1983 and the data input at delivery, in December 1983. The input when the mother left hospital after delivery was introduced in January 1984 and ICD coding has been carried out since November 1984.

Hardware and software

An ICL DRS 20/50 distributed microcomputer system has been used with four 'intelligent' terminals networked together (one on the labour ward, one on the postnatal wards, and two in the obstetric secretaries office) with a dot matrix printer at each location. Data storage is on a 27 mb disc, with daily back-up onto a tape streamer. With installation and wiring the system cost approximately £20 000. The ICL DRX operating system is used, programming being done by the Regional Computer Centre using Cis Cobol.

Data inputs and outputs

The first data entry onto the system is by the obstetric secretaries from information abstracted from the structured case notes after the first antenatal clinic visit (Fig. 1). Three consecutive screens of questions (frames) are answered and this allows the automatic production of a letter for the general practitioner. In this, booking for delivery is confirmed, the type of antenatal care (hospital or shared) is proposed and risk factors such as previous low-birthweight baby, which are derived from the data entered, are highlighted. A list of women due to be delivered each month is produced regularly from the booking data.

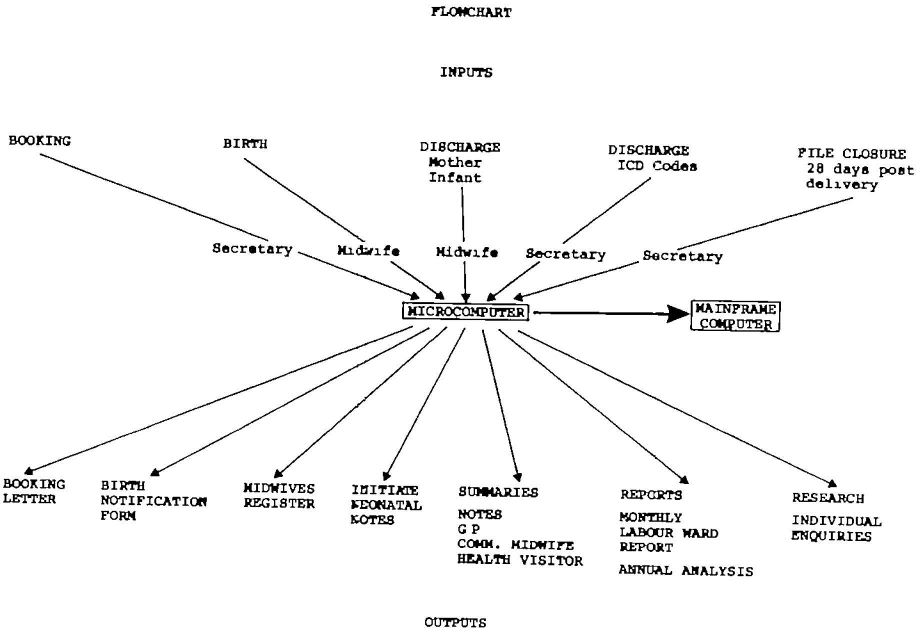

Fig. 1. Flowchart showing points during pregnancy and after when data is entered and the use which can be made of that data.

Whenever a woman is admitted to the maternity unit, data needed to produce the standard HMRI form (date, method and source of admission) are entered by a midwife using the labour ward terminal and a print-out of the form is produced. When a woman is in labour, one frame of antenatal investigations and one of antenatal complications are completed by the midwife, and after delivery she completes four more frames of details of labour and delivery. There are many cross checks validating data entry and all dates and times are checked using the real time clock facility. A page for the labour ward register is produced and birth notification forms printed as a batch every day.

When a mother leaves hospital after delivery the midwife completes four frames of data relevant to the puerperium and the newborn infant at a terminal on the post-natal ward floor. With this further entry a discharge summary is printed for the community midwife. This is passed on to the health visitor 10 days later, as is a form to be returned at 28 days by the health visitor, confirming that the baby is alive. The day after discharge, a secretary prints copies of the discharge summaries adapted for the general practitioner. These are dispatched after being checked and signed by a senior house officer. A secretary then runs the International Classification of Diseases (ICD) programme which automatically derives many ICD codes from patient data already on file. She adds and amends as necessary aided by an obstetric coding extract (Scottish Health Service Common Services Agency). The file for a mother and baby is closed when the form from the health visitor is received. A program is run monthly to list the number of women who are still undelivered 4 weeks after their estimated date of delivery. For those women who experience spontaneous abortion or who are transferred to other centres, the 'antenatal-only' record completion program is used.

Table 1. Abstract from a monthly report for the labour ward and regional statistics

Deliveries for December 1985	
Total no. of women delivered	205
Total no. of primigravida	102
Total no. of babies born	207
Total no. of babies weighing <2500 g	22
Total no. of babies weighing <1000 g	2
Perinatal mortality	
Antepartum stillbirths	0
Intrapartum stillbirths	0
Neonatal deaths	2
No. of singleton deliveries	203
Spontaneous deliveries	148
Instrumental deliveries	23
Caesarean deliveries	30
Inductions	13
Epidurals	44
Post-partum haemorrhages	20

Other reports

A monthly audit report is produced, which contains labour ward information of interest to local obstetricians and midwives and data required for regional statistics (Table 1). Data are transferred to the regional mainframe computer on an annual basis enabling the Standard Maternity Information tabulations, (available from the Northern Regional Health Authority Computer Centre) to be produced and the Hospital Inpatient Enquiry (HIPE). In addition, data has been transferred to a mainframe computer at London University for research purposes.

Data validation

Each data item on computer file for 253 consecutive deliveries was validated by one obstetric secretary against the notes. For this she used the enquiry program which allows one to scroll through the screens without altering data items. Inconsistencies were reviewed by one of us (M.M.) and the error rates calculated for each data item.

ICD assessment

The secretary responsible for doing ICD coding kept a record of 500 consecutive cases. For these she assessed the number of codes which were not automatically generated and needed to be added manually.

Results

Hardware and software

There has been one hard disc 'crash' and although the disc was replaced within 24 h, the tape streamer was not in use at this time and regeneration of the hard disc from the back-up floppy discs took a further 6 h. On one occasion, a socket, which was not being used on the network, had its terminal plug removed and this disabled the network although the central model 50 remained functional. On two further occasions, programs would not load, but the service engineers arrived within 3 h of being called. Whilst the system was down, birth notification and discharge data were entered on paper copies of the screens for subsequent entry onto the computer. On the two occasions when there has been a temporary power failure, no breakdown or loss of data occurred. Occasional mechanical problems with the printers have occurred, but the operating system allows outputs to be directed to other printers causing only a slight inconvenience until the problem is rectified. No significant software faults have arisen and a number of program enhancements have been introduced.

Data input

No formal training was necessary for the midwives. It is difficult to specify an average time taken for inputting data since the terminals are in busy places with the result that data entry is often disturbed by such interruptions as telephone calls. Times, without interruption, are approximately: registration and booking 4–7 min, admission order entry and print-out 2–3 min, antenatal complications and investigations 3–4 min, birth notification and register print-out 6–10 min, and discharge entry and print-outs 4–6 min.

Outputs

The letter sent to the general practitioner after booking was improved in a number of ways during 1984 as a result of suggestions made by general practitioners. For example, the wording has now been made clearer when the practitioner's offer of shared care is declined. In an initial assessment (Maresh 1984), the highlighting of risk factors was noted to have detected many potential clinical problems that had tended to be overlooked such as a previous low-birthweight infant. The birth notification forms are acceptable to the District and Region. The automatic production of relevant data has eliminated the need for a manually completed midwifery register and this has saved considerable time. The summary for the general practitioner is dispatched within 48 h of discharge (except at weekends), and the mother is able to take home a copy with her for the community midwife. These are more legible than the handwritten copies used previously.

Reports and data analysis

A report on labour ward activity is produced monthly by the computer. In 1983, this was derived from the hand filled register, as well as a similar report being produced by the Commodore PET system. There were always errors in the manually produced report, for example one month breech deliveries were under reported by 50%. The monthly report (Table 1) requested, by the regional perinatal epidemiologist is now returned more quickly and accurately than from hospitals using a manual system. The report includes a breakdown by birthweight, vital for perinatal epidemiology, but tedious to collect manually. From these individual returns an annual analysis of all maternity units in the Region is currently produced.

An *ad hoc* enquiry program allows cases to be listed which have certain characteristics so that total numbers can be obtained and case notes obtained for review (Table 2). From the transfer of data to the Regional Computer Centre the Standard Maternity Information System tabulations have been obtained, as has the Hospital Inpatient Enquiry (HIPE) which was required up until the end of 1985. Assessment of new tabulations on a university mainframe computer is allowing a new set of annual tabulations to be designed and an example showing perinatal morbidity indices associated with maternal age is shown in Table 3.

Table 2. An example of an *ad hoc* enquiry for ethnic groups of mothers of Indian Pakistani and Bangladeshi origin delivered during 1984

```
                YEARLY ARCHIVE FILE ENQUIRY
Enquiry on year 1984 for months 01 to 12—selecting
on all births
Codes selected:
           04 ethnic group          equal to I
2370 records have been read from the archive file
2370 records (100·00%) were extracted for selection
     comparison
 246 records (10·38%) were selected
   0 records (0·00%) held missing values
```

Table 3. An example of a table currently being assessed for inclusion in a new annual report showing perinatal morbidity indices associated with maternal age

Maternal age	Fetal acidosis pH<7·25%	Apgar <7 at 5 mins %	Infant intubation %	Gestation <38 weeks %	Birth weight <2500 g %	Admitted SCBU >24 hrs %	Congenital malformns %	Perinatal deaths n
<20 n=213	1·4	2·8	8·5	18·8	13·2	5·6	6·8	4
20–24 n=699	1·6	2·3	6·9	12·5	9·0	4·3	7·4	10
25–29 n=709	1·0	2·5	7·0	11·3	7·3	5·1	4·8	6
30–34 n=560	2·0	1·1	5·0	11·8	6·4	5·0	9·4	4
>35 n=293	2·7	2·7	9·9	14·0	6·5	5·8	5·4	0

Data validation

Only 13 of the 160 data items had an error rate of 1% or more. Comments on those with the highest rates and some proposed solutions are shown in Table 4. Items that are known to be difficult to collect accurately such as whether the membranes were artificially ruptured or not, and mode of onset of labour, had an error rate of only 1–2%.

ICD coding

The ICD code generation program could derive 68 of the codes from the clinical data entered. Despite this being only a minority (about 15%) of the total number of obstetric codes these were the most common and in the assessment of 500 cases 92% of the required codes were derived.

Manpower and costing

The introducton of the information system has saved secretarial time. Previously the secretaries had been unable to do all the summaries and many had been sent to a central typing pool. Now a junior and senior secretary are able to deal with letters and summaries for all the deliveries in addition to their usual workload. The midwives do not save any time on the production of the birth notification form, but they no longer have to complete the midwifery register manually. They have the added benefit of easy access to information on individual patients and they now receive a regular audit of labour ward practice. A saving in salaries has been achieved as two part-time midwives are no longer required to keep the midwifery register and to liaise with the community midwives. A further saving in time has been achieved since the medical records staff no longer need to record information for the Hospital In-Patient Enquiry (HIPE). A true 1 in 10 sample has now been automaticaly obtained from the system, which can be converted to 100% coverage as required for Korner. It is difficult to be precise about the cost of the previous manual system, since some of the forms and the registers had been bought in bulk some years before, but the cost of the stationary required for the new system is approximately 30 pence per case. The District Health Authority has agreed to take on

Table 4. Data items with error rates of 3% or more in 253 consecutive case notes cross checked against the computer file. Also shown are comments and proposed solutions

Data item	Error rate (%)	Comment	Proposed solution
Proteinuria	5	Misunderstanding of definition on screen	Definition reworded: check message
Number of previous terminations	4	Temporary secretary not instructed in distinguishing therapeutic from spontaneous abortion	Improved training
Number of antenatal visits	3	Number taken from Co-op card including GP visits	Definition reworded
Maximum antenatal blood pressure recording	3	Worst error 70 for 90	Definition reworded

the revenue consequences for stationary and a hardware maintenance contract of £2400 per annum.

Discussion

Our major objective has been to improve the care of the mother and baby by using a computer system for collecting accurate and complete data for dissemination to the primary health care team and planners. The system has met the main requirement of the Korner committee by collecting a recommended data set. By using modern computer technology, without any increase in staff, it also meets further requirements by linking into the regional mainframe computer and the Child Health System, assisting in operational tasks such as the production of forms, and avoids duplication of data entry and outputs.

The system relies heavily on midwives for data entry. Our midwives have remained enthusiastic about the system since it reduces repetitive form filling and, for the first time, provides them with readily available information on all women booked for delivery. This is invaluable when notes are lost and for dealing with telephone requests for information from general practitioners, health visitors and community midwives. Better communication with general practitioners, community midwives and health visitors is likely to improve the shared antenatal care system and encourage an early visit to the mother and her baby on return home from hospital. General practitioners have been pleased by the rapidity with which summaries reach them. Hospital medical staff no longer have to dictate routine letters and summaries. The care of the woman and her baby has improved through the highlighting of risk factors, often overlooked by busy clinicians in routine antenatal clinics, and by the use of clinical prompts, as in the case of rubella-susceptible women needing vaccination in the puerperium.

Our investigation showed a high degree of data accuracy between the computer and the clinical records. This results from the extensive on-line validation of the data as they are entered, and the use of the most informed person to enter the data, as for example in the discharge input, when it is done by the midwife who actually discharges the woman and her baby. A few problems were found in our investigation of the accuracy of the system and these have been rectified. A more detailed assessment has now been carried out at Hillingdon Hospital. A link with the patient administration system is being developed which will decrease the volume of data entered when the woman books for care at the antenatal clinic. A further development, which should be available by late 1986, is a detailed neonatal intensive care module. The data collected on babies admitted for special care will allow assessment of current practices. It will also enable a comparison to be made between babies whose mothers were booked locally, or were transferred *in utero* or post-natal transfers, since the last mentioned is not ideally covered in the current system.

A realistic cost-benefit analysis is difficult to achieve because of balancing the cost of the hardware and those employed to run it, against the considerable savings achieved by eliminating many of the tasks carried out by hand. The cost of the hardware spread over 5 years, together with the maintenance contract, is less than a clerical officers salary (allowing for employers contribution and the London allowance). The saving of time by the midwives, secretaries and medical records staff could theoretically add up to one person's salary. However, it must also be recognized that the system is likely to improve care significantly and this is difficult to cost.

We have now obtained a highly detailed and accurate data set from deliveries over 2 years. Transfer of the data onto the regional mainframe computer has allowed a standard package of maternity tabulations to be produced. By transferring onto a mainframe computer at London University we are evaluating a new detailed set of tables which allows the auditing of antenatal, intrapartum, puerperal and neonatal care. The tabulations specify the particular characteristics of the hospital population so that, when managerial techniques such as performance indicators are applied, valid inter-hospital comparisons can be made. For example one can not compare caesarean section rates from a suburban district general hospital with those from a inner city referral unit, since the latter will have a higher primiparous population and a significant *in utero* transfer rate, both of which factors increase caesarean rates. Currently the DHSS performance indicators are of limited value in obstetrics since so few data are available, but with the new data set we are now assessing new indicators. Once the users have agreed on the set of tabulations a program will be written so that an annual report can be produced in the obstetric unit without using a mainframe computer.

The St Mary's system has now been introduced into other Districts, and Hillingdon Hospital had a phased introduction of the system during 1984 with the full system running by 1st January 1985. Luton and Dunstable Hospital was fully operational by June 1985. The capital for installing the system into all the other maternity units in the North West Thames Region by 1987 has been provided by the Region and currently all except one are committed to taking on the system. Eventually this will provide the Region with detailed information on all the 46 000 births occurring every year, thereby giving vital pointers for planning decisions and providing the basis for an annual survey of the maternity services at a Regional, District and Unit level, soon after the end of each year. In addition through the use of the mother's postcode, analysis will be available by district of residence. Now that the system has been recommended by the Computer Policy Committee (1985) there has been much interest from other regions and districts who plan to implement the system.

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Uptake of amniocentesis in women aged 38 years or more by the time of the expected date of delivery: a two-year retrospective study

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Summary. The uptake of amniocentesis for the prenatal diagnosis of chromosome abnormalities in older women ($\geqslant$ 38 years by the time of the expected date of delivery) is reviewed over a 2-year period. Overall, 41·3% of women were not tested, including a group of 7% in whom no record of discussion of prenatal diagnosis could be found on review of obstetric records. Refusal of the offer of amniocentesis and late booking were significantly greater in Asian women ($P < 0{\cdot}01$). One-third of chromosomally-abnormal infants were not detected antenatally in the study group.

Prenatal diagnosis is now widely available for the diagnosis of chromosome anomalies. The commonest indication for fetal karyotyping is the increased risk of a Down's syndrome pregnancy in older women (Penrose 1933). Amniocentesis is currently the usual procedure for obtaining cells for fetal chromosome analysis and was first described for this indication by Jacobson & Barter (1967).

The uptake of amniocentesis by eligible women appears to be steadily increasing (Baird *et al.* 1985). This study aimed to assess retrospectively the uptake of amniocentesis in the local population and the reasons why some women were not tested. We also wished to discover any particular characteristics of patients who did not have a prenatal diagnosis.

Amniocentesis is an accurate but expensive test yielding a low percentage of abnormal findings. Crude costing analysis has shown the test to be worthwhile in older women (Hagard & Carter 1976) and age is still the most widely used criterion upon which to offer amniocentesis. This study was therefore performed using only the records of those women who should have been offered amniocentesis according to the unit policy of offering the test to women who would be aged 38 years or more by the expected date of delivery.

The fetal and maternal risks of amniocentesis have been reviewed several times (NICHD, 1976; MRC Working Party, 1978; Sant-Cassia *et al.* 1984) with conflicting conclusions as to its safety and specific hazards. During counselling the risks of the procedure are always explained to the patient, and this is often the reason why the offer of antenatal diagnosis is not accepted. Most authorities now accept that uncomplicated amniocentesis carries approximately a 0·5% risk of fetal loss (Philip & Bang 1978; Rodeck 1984), and there are also reports of other slight risks, including premature rupture of the membranes, respiratory problems at birth and congenital dislocation of the hip (MRC Working Party 1978).

Much work has been done to try to improve the safety of amniocentesis. Location of the placenta in ultrasound-controlled procedures has been shown to reduce procedural complications (Karp *et al.* 1977; Kerenyi & Walker 1977) and

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more recently an ultrasound guided technique (Romero *et al.* 1985) has been introduced. This technique, which displays the needle throughout insertion, is currently in use at University College Hospital (UCH) but in the period covered in this report the ultrasound-controlled technique was used, with scanning only before the needle was inserted.

Patients and methods

The study group consisted of all patients aged 38 and over who were delivered at UCH between January 1983 and December 1984, inclusive. In addition the booking records were checked so as to include all patients in this age category who had been seen and therefore were eligible for amniocentesis. Terminations of pregnancy and spontaneous abortions after 16 weeks were included but transfers from other hospitals were excluded.

At their initial booking visit all women eligible for amniocentesis were referred to a special genetic and ultrasound clinic unless they were either too late for amniocentesis (more than 20 weeks gestation) or they were definitely not interested in prenatal diagnosis. Ideally patients were seen in this clinic between 16 and 18 weeks gestation for counselling and amniocentesis if requested. Amniocentesis was performed by the standard ultrasound-controlled method using a disposable 22 gauge needle to withdraw 20 ml of amniotic fluid. After removal of the needle the uterus was rescanned to check the fetal heartbeat and reassure the patient.

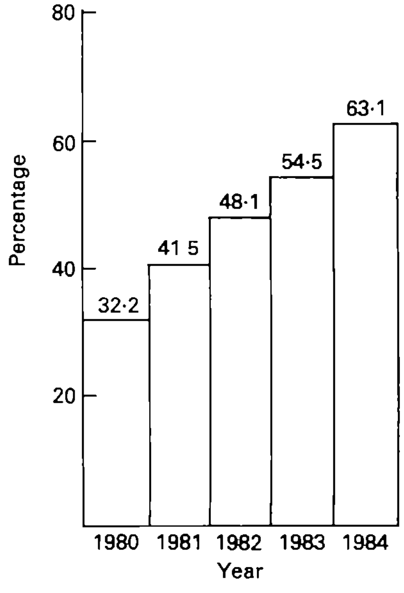

Fig. 1. Uptake of amniocentesis by women aged ≥ 38 years at the time of delivery (1980–1984).

Data regarding all patients delivered at UCH are stored on a computer (DEC PDP 11/70). These records were cross checked with those of the genetic clinic and the antenatal notes of any patient who did not have amniocentesis were examined to ascertain the reasons for their not being tested. The ethnic group of all patients in the study was recorded and related to the uptake of amniocentesis.

Statistical analysis of the data was by the χ^2 test using Yates' correction.

Results

Figure 1 shows the uptake of amniocentesis at UCH for the years 1980–1984. During the two years covered in the study there were 286 patients who fulfilled the above criteria and were eligible for the study. The overall uptake of amniocentesis during the two years 1983 and 1984 was 58·7% (Table 1). The uptake of amniocentesis by different ethnic groups is shown in Table 2. The reasons recorded for no amniocentesis having been performed are shown in Table 3. Of 63 patients refusing the offer of amniocentesis, 29 were counselled in the genetic clinic and 34 expressed no interest in prenatal diagnosis when seen in the antenatal clinic and were therefore not referred to the genetic clinic. Late booking was significantly higher in the Indian, Pakistani and Bangladeshi (Asian) population when compared with the Europeans (χ^2 = 11·1675, P<0·01), and the uptake of amniocentesis in this group was significantly lower (χ^2 = 30·5725, P<0·001) among those attending in time for prenatal diagnosis.

In 20 patients (7%) during the two years there was no mention in the obstetric record of amniocentesis having been discussed or the offer of referral to the genetic clinic having been made. Once again this was significantly more common in the Asian group than in the European (χ^2 = 9·2479, P<0·01). A total of 168 patients underwent 173 amniocenteses because five cultures failed to grow necessitating a repeat procedure, but only in one instance was no result obtained after two taps. Thus 3·45% of cultures failed. In no patient was there a failure to obtain amniotic fluid.

Six chromosomally abnormal fetuses were

Table 1. Uptake of amniocentesis by women aged ≥ 38 years at the time of delivery at UCH, 1983–1984.

	Year		
	1983	1984	Total
Amniocentesis	79 (54·5%)	89 (63·1%)	168 (58·7%)
No amniocentesis	66	52	118
Total	145	141	286

diagnosed by amniocentesis; three had trisomy 21 and there were three others. Five of these abnormal pregnancies were terminated, but one patient with a Down's syndrome fetus elected to continue the pregnancy. In the group of 118 patients who did not have an amniocentesis a further three pregnancies resulted in infants with Down's syndrome, but there were no other chromosome abnormalities diagnosed at delivery. Thus two-thirds of the chromosome abnormalities were detected antenatally in the population eligible for screening.

Discussion

The overall uptake of amniocentesis (58·7%) is higher than in previous years (Fig. 1) and follows the trends reported by Baird *et al.* (1985). This rate is still well below that in Denmark where as many as 80–85% of eligible women have been tested (Diernaes & Filtenborg 1982). Of the European women in this study 66·2% elected to have amniocentesis and this is a higher proportion than in many other studies. The overall uptake of amniocentesis may be lower at UCH because of the relatively higher proportion of Asian women (13%) in the older pregnant population (Fig. 2) who tend to have strong religious objections to antenatal diagnosis. The uptake of amniocentesis has previously been noted to vary with ethnic origin (Adams *et al.* 1981) and this is confirmed in our study. As uptake of prenatal diagnosis increases, the detection of Down's syndrome fetuses in the older population will improve, but even with 100% uptake in all women aged ≥ 38 years at delivery only 20% of all Down's syndrome fetuses would be detected antenatally (Cuckle *et al.* 1984). Additional criteria such as low maternal serum α-fetoprotein levels have been suggested to broaden the range of women to whom amniocentesis should be offered (Merkatz *et al.* 1984).

The incidence of late booking is significantly higher in Asian women than in Europeans. A programme of re-education of these women would therefore enable a proportion of at-risk patients to attend earlier for counselling. The incidence of refusal to accept prenatal diagnosis is also significantly increased in this group, so the problem of late booking may not prove to be so important as regards improving numbers for uptake of amniocentesis. Late booking has, however, been associated with other pregnancy risks and poor obstetric performance and therefore encouragement for this population to book earlier in pregnancy is desirable. One obvious problem is the language barrier and therefore the hospital has employed two Bengali health counsellors full time since June 1983. As a result of this, lack of communication is unlikely to be a cause of poor uptake of amniocentesis in this group.

Perhaps the most disturbing finding from this study was that in 7% of patients eligible for amniocentesis there was no documented evidence in the patients' obstetric records of prenatal diagnosis ever having been discussed; a serious omission. Among the group of uncounselled patients there was once again a highly significant increase in the proportion of Asian women. Partly as a result of this finding, but also to try to see patients earlier to discuss first tri-

Table 2. Uptake of amniocentesis by ethnic group at UCH, 1983–1984.

	European (*n* = 216)	Asian (*n* = 37)	Other (*n* = 33)	All patients (*n* = 286)
Amniocentesis	143 (66·2%)	6 (16·2%)	19 (58·7%)	168 (58·7%)
No amniocentesis	73	31	14	118

Table 3. Reasons for amniocentesis not having been performed in women aged ≥ 38 years at the time of delivery, 1983–1984

Reason	European	Asian	Other	All patients
Refused offer of amniocentesis	45	9	9	63
Late booking (after 20 weeks)	11	15	1	27
Advised against amniocentesis	6	0	0	6
Miscellaneous*	2	0	0	2
No recorded offer of amniocentesis	9	7	4	20
Total	73	31	14	118

* One patient abroad from 14 to 36 weeks. One patient did not attend for amniocentesis.

mester diagnosis, the older women are now seen in a special booking clinic within one week of referral and counselled by a doctor on their first visit to the hospital. Almost all eligible patients will attend this clinic and consequently the uptake of prenatal diagnosis should increase.

One reason that the uptake of amniocentesis is lower than expected may be the timing of the test. Late termination of pregnancy carries a greater risk than first trimester termination (Turnbull & Mackenzie 1983) and is also less acceptable to the patients. This also contributes to the lower than expected reduction in the birth incidence of Down's syndome since the widespread introduction of amniocentesis (Ferguson-Smith 1983). The introduction of first trimester diagnostic methods such as chorionic villus sampling may increase the uptake of prenatal diagnosis by older women and thus help to further reduce the birth incidence of Down's syndrome. There will always be a percentage of women who do not wish to have prenatal diagnostic tests, but we must aim to have a system whereby all eligible women at least have an opportunity to make an informed decision.

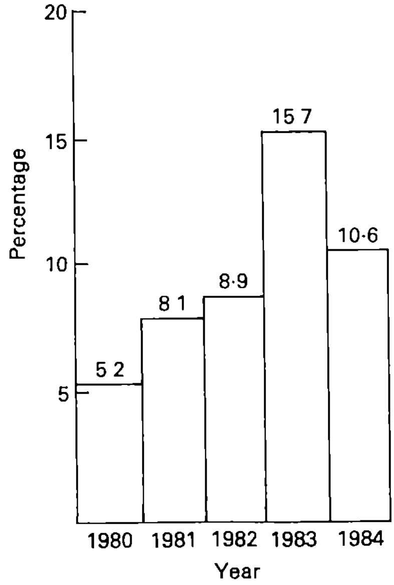

Fig. 2. Percentage of Asians in the women aged ≥ 38 years at the time of delivery (1980–1984).

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Immunosuppressive properties of pregnancy serum on the mixed lymphocyte reaction

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Summary. The human fetus may escape immunological attack because of serum factors which have immunomodulatory influence on maternal cellular effector responses. Paired peripheral and retroplacental sera were shown to inhibit the allogenic mixed lymphocyte reaction (MLR) used as an in-vitro model of cell-mediated immunity. There was no correlation between the suppressive effect of the peripheral and retroplacental sera and the serum concentrations of four pregnancy-related proteins (α-fetoprotein, pregnancy-associated α_2 glycoprotein, pregnancy-associated plasma protein A and Schwangerschaftsprotein 1) to which immunosuppressive properties have been ascribed, but there was a negative correlation between peripheral AFP and MLR inhibition ($r = -0{\cdot}62$, $P < 0{\cdot}001$). Hence, the factor or factors responsible for suppressing the MLR are not those investigated in the present study.

The reasons for human fetal allograft survival are probably multifactorial. Altered maternal immune reactivity by serum factor(s) having immunomodulating activity is one possibility currently in favour. There is general agreement that systemic maternal immunocompetence is not significantly depressed in pregnancy (Clemens *et al.* 1979) but that non-specific immunosuppressive factors may be acting to prevent fetal allograft rejection locally because of their high concentration at the fetoplacental site (Clemens *et al.* 1979; Siteri *et al.* 1977). Some of these factors have already been defined such as steroids, human chorionic gonadotrophin (hCG), and various pregnancy-related glycoproteins (Klopper 1982). Others have been found in the supernatants or extracts of trophoblast cultures, but are as yet unidentified (Kouttab *et al.* 1976). They are thought to act in several ways: by affecting immune recognition of alloantigens by lymphocytes (Albrechtsen *et al.* 1977), on lymphocyte transformation as in the mixed lymphocyte reaction (MLR) (Jones *et al.* 1973) or by inducing suppressor cells either directly or indirectly (Voisin 1980; Segal *et al.* 1980).

Although most of these substances have been shown to inhibit lymphocyte function *in vitro* this does not necessarily correlate with any functional role *in vivo*. The assessment of depressed cell-mediated immunity *in vitro* during pregnancy is based on the ability of pregnancy serum to inhibit lymphocyte transformation in the MLR. This is quantified by measuring the amount of radiolabelled thymidine incorporated into actively dividing lymphocytes. Since some of these serum factors are thought to be immunosuppressive at relatively higher concentrations than is normally found in the general circulation, we measured the levels of four pregnancy proteins; SP1 (Schwangerschaftsprotein 1), α_2PAG (pregnancy-associated α_2 glycoprotein), PAPP-A (pregnancy-associated plasma protein A) and AFP (α-fetoprotein) in paired retroplacental and peripheral blood sera and looked for any correlation between the

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serum concentration of protein and the inhibitory effect on the MLR.

Patients and methods

The study included 23 pregnant women at between 34 and 42 weeks gestation who were about to undergo elective caesarean section under either epidural or spinal anaesthesia. They were aged 16–39 years (mean 27 years) and six were primigravidae. Paired peripheral and retroplacental blood samples were taken during the operation and then centrifuged at 1000 r/min for 10 min. Retroplacental blood was collected by aspirating the blood with a quill attached to a syringe from the space between the maternal decidual surface and the partially separating placenta. The serum was collected and stored at −20°C.

Protein assays

SP1. Nunc Immunoplate I plates were sensitized with F(ab$^-$)$_2$ rabbit anti-human SP1 antiserum (Dako Laboratories) diluted in PBS-azide, and incubated overnight at 4°C. Plates were washed three times in PBS-Tween 20 and appropriately diluted test samples or standards were added for 3 h at 37°C. After a further three washes in Tween 20, alkaline phosphatase (Sigma) conjugated to rabbit anti-human SP1 (Dako Laboratories) was added for 2 h at 4°C. After two more washes in PBS-Tween 20 and one in distilled water, the plates were incubated for 20 min at 37°C in paranitrophenyl phosphate substrate (Sigma). The reaction was terminated with the addition of 3 mol/l sodium hydroxide and the absorbance read at 405 nm on a multiscreen ELISA microtitre plate reader (Flow Laboratories).

α_2 PAG. Assay plates were sensitized with F(ab$^-$)$_2$ sheep anti-PAG antiserum (Seward Laboratories) for 4 days at 4°C. Pre-diluted serum samples or standards were incubated at 4°C overnight followed by rabbit anti-α_2-PAG (Dako Laboratories) for 2 h at 4°C. After three more washes, alkaline phosphatase conjugated goat anti-rabbit IgG (Miles Laboratories) was added for 2 h at 4°C. Substrate was added as for the SP1 assay, allowed to develop, and the reaction was terminated with 3 mol/l sodium hydroxide. The colorimetric reaction was read on the ELISA reader at 405 nm.

In both the SP1 and α_2PAG ELISA assays, internal standards of pregnancy reference serum (Seward Laboratories) were diluted in PBS-Tween 20 and standard curves constructed of absorbance against pregnancy protein concentrations.

PAPP-A. Serum samples were kindly assayed by Dr A. Bolton using a radioimmunoassay developed at the North East London Polytechnic.

AFP. Radioimmunoassays were performed in the Clinical Chemistry Department at Guy's Hospital. The test samples were appropriately diluted and compared against a known standard of serum containing AFP (reference sample 72/227) supplied by the National Institute of Biological Standards and Controls.

Lymphocyte separation

Mononuclear cells (MNC) were separated as described previously (Nicholas *et al.* 1984) using a density gradient technique based on the method of Boyum (1968).

Mixed lymphocyte reactions

Mononuclear cells were separated, counted and adjusted to a concentration of 10^6/ml. Equal numbers of cells were taken from each donor so that the total number of cells per well was 2×10^5. All experiments were performed in flat-bottomed wells (Titertek).

Thymidine incorporation

Lymphocyte proliferation was quantified by the amount of tritiated thymidine (^{3}HTdR) incorporated into the activated lymphocytes as described previously (Nicholas *et al.* 1984).

Pooled normal serum

Blood was obtained from 10 healthy male medical students, serum was separated and frozen at −70°C. To ensure the normality of the serum samples each was tested for its ability to support lymphocyte proliferation in the MLR. Analysis of the results showed that they were normally distributed at the 5% level (Fillibens correlation coefficient 0·98, data not shown). The sera were then pooled and used as pooled

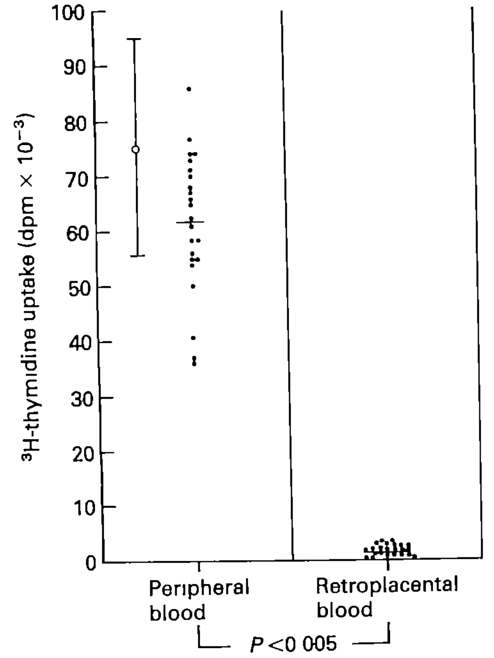

Fig. 1. The effects of paired peripheral and retroplacental sera at 10% v/v in the mixed lymphocyte reaction measured by thymidine uptake. Horizontal bars denote the means and ⫯ the mean ± SD tymidine uptake with pooled normal serum. The difference between the means is significant $P < 0{\cdot}005$.

normal serum (PNS) in subsequent experiments.

Calculation of ELISA results

Concentrations of SP1 and α_2PAG in serum samples were calculated using a computer program written in Applesoft Basic to run on an Apple II Europlus computer. Briefly, the program constructs the best fit between absorbance and protein concentrations of known standards. It then automatically calculates the mean and standard deviation for each test sample.

Statistical analysis

Since the data were found to be normally distributed by Filliben's test, the Student's *t*-test was used and values of $P < 0{\cdot}05$ were considered to be significant. Correlation coefficients were calculated according to standard procedures.

Results

Mixed lymphocyte reaction

Figure 1 is a scatter diagram comparing the effects of paired peripheral and retroplacental sera at 10% v/v in the MLR. Only seven of the 23 (30%) pregnancy peripheral serum samples were inhibitory when compared with pooled normal serum which was used as the control. Inhibition was recorded when the amount of cellular proliferation (as measured by thymidine uptake) was >1 SD below the mean proliferation produced by the pooled normal serum. In contrast, all 23 retroplacental sera were inhibitory in the MLR.

Serum protein estimations

The mean concentrations and ranges of the four pregnancy proteins assayed in the paired retroplacental and peripheral sera are shown in Table 1. There were no statistically significant differences in the mean levels of SP1, PAPP-A and α_2PAG between paired serum samples. But the mean serum AFP concentration was significantly higher in retroplacental blood than in peripheral blood ($P < 0{\cdot}005$).

Table 1. Concentrations of four serum proteins in 23 paired retroplacental and peripheral sera

	Retroplacental serum		Peripheral serum	
Serum protein	Mean (SD)	Range	Mean (SD)	Range
Schwangerschaftsprotein 1 (μg/ml)	217 (213)	30–878	193 (103)	28–350
Pregnancy-associated plasma protein-A (μg/ml)	133 (98)	34–409	158 (97)	0–278
Pregnancy-associated α_2 glycoprotein (μg/ml)	1616 (1500)	59–8000	794 (600)	11–2643
α-Fetoprotein (kU/l)	3650 (1250)*	120–8274	143 (100)*	23–400

* Difference between paired sera statistically significant ($P < 0{\cdot}005$)

Correlation between serum proteins and MLR inhibition

There was no correlation between the peripheral and retroplacental serum levels of α_2PAG, SP1 and PAPP-A and their ability to inhibit the MLR, but there was a negative correlation between serum AFP and MLR inhibition ($r = -0{\cdot}62$, $P < 0{\cdot}001$; Fig. 2).

Discussion

The aim of this study was to investigate the relation between the inhibitory effect of pregnancy sera in the MLR and the serum concentrations of pregnancy-related proteins. We found that all retroplacental sera were inhibitory in the MLR in contrast to only 30% of the paired peripheral serum samples. This is probably a reflection of the high production of factor(s) locally at the feto-maternal interface spilling into the general circulation. This inhibitory activity is not due to cytotoxicity because interleukin-2 can reverse the inhibition (Nicholas *et al.* 1984). We found no correlation between three of the four serum proteins assayed (SP1, α_2PAG, and PAPP-A), and MLR inhibition. However, with AFP, there was a negative correlation between the peripheral serum concentration and the MLR inhibitory capacity. The immunoregulatory role of AFP in man has always been in dispute. Numerous groups have apparently demonstrated inhibition of lymphocyte transformation *in vitro*, following mitogenic or allogeneic stimulation (Murgita & Thomasi 1975; Yachnin & Lester; Figueredo *et al.* 1979). Adinolfi (1982) could not confirm these findings and reported that some preparations had an apparent suppressive effect whereas in others AFP appeared to stimulate lymphocytes *in vitro*. Our results confirm the view that AFP is not immunosuppressive. We are now investigating the nature of these MLR inhibitory pregnancy factor(s) which appear to be different from those currently recognized.

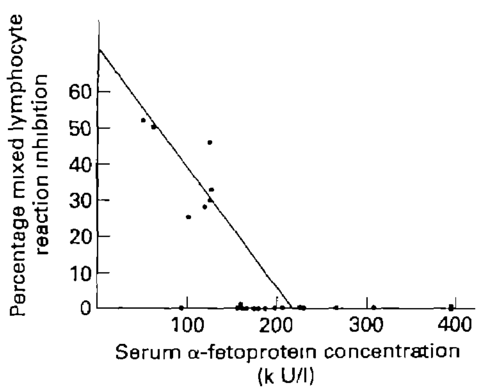

Fig. 2. Correlation between peripheral serum α-fetoprotein concentration and inhibition in the mixed lymphocyte reaction. There is a statistically significant negative correlation ($r = -0{\cdot}62$, $P < 0{\cdot}001$)

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The predictive value of fetal breathing movements in the outcome of premature labour

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Summary. Fetal breathing movements (FBM) were assessed in 28 pregnant women, presenting with uterine contractions before 34 weeks gestation. External tocometry was used to determine uterine contractions objectively. The first group consisted of 17 patients, treated by tocolytics after the ultrasound scanning showed absence of FBM. The second group comprised 11 patients with FBM present, who were observed only. In the first group nine women were delivered within 1 week, whereas in the second group no patient was delivered in that period, all of them being discharged. In patients with premature contractions the presence of FBM seems to indicate that the pregnancy will continue while absence of FBM foreshadows early delivery.

Prematurity still remains the main cause of perinatal morbidity and mortality; however, the identification of preterm labour is often presumptive. It is accepted that in up to 50% of women in apparently established preterm labour, contractions subside spontaneously, and pregnancy continues (Anderson 1981). Treatment given for uterine tocolysis is therefore unnecessary in many cases. In an attempt to predict the outcome, Castle & Turnbull (1983) were the first to demonstrate that the presence or absence of fetal breathing movements (FBM) might suggest whether or not preterm labour would progress.

The purpose of the present study was to confirm the results of Castle & Turnbull (1983) and to investigate the efficacy of pharmacological treatment where the absence of FBM might indicate the inevitable progression of labour.

Patients and methods

The study included 28 pregnant women presenting consecutively at the obstetrics department of Hillel Jaffe Memorial Hospital complaining of uterine contractions before 34 weeks gestation. The pregnancies were singleton, uncomplicated and with intact membranes and the exact date of the last menstrual period was known.

On admission each patient had a thorough gynaecological examination including a Bishop score assessment. External tocometry for 1 h was used to determine uterine activity. FBM were assessed by two fully experienced ultrasonographers using a Pie Data Medical real time ultrasonic scanner (scanner 400).

Fetal breathing, detectable as regular downward movements of the diaphragm with paradoxical movements of the fetal chest and abdomen, was considered 'present' if sustained for ≥20 s and 'absent' if no sustained movements could be detected over at least 45 min (Castle & Turnbull 1983). Patients in whom FBM could not be detected were given 50 g of dextrose orally to enhance FBM (Trudinger *et*

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Table 1. Characteristics of 28 women with premature onset of labour in the presence or absence of fetal breathing movement (FBM)

	FBM	
	Present	Absent
No. of patients	11	17
Age (years)	27·2 (0·8)	28·4 (0·6)
Nulliparae (*n*)	2	4
Gestational age on admission (weeks)	31·5 (0·4)	30·3 (0·4)
Presentation		
Vertex	10	15
Breech	1	2
Bishop score		
≤5	11	12
>5	—	5

Results are numbers of patients or means (SD) as appropriate.

al. 1979), and the ultrasound examination was repeated 30 min later.

The patients were categorized into two groups according to the presence of FBM.

Group 1. Patients in whom FBM were absent received tocolytic treatment with ritodrine hydrochloride (Yutopar) given by intravenous infusion at an initial dose of 0·05 mg/min and gradually increased by 0·05 mg/min every 10 min until arrest of contractions. If delivery did not take place within 72 h, FBM were reassessed.

Group 2. Patients in whom FBM were demonstrated were hospitalized; the Bishop score and external tocography were estimed every 12 h till uterine contractions subsided spontaneously. Ritodrine was to be given if uterine contractions strengthened or the Bishop score increased.

Results

Uterine contractions were confirmed by external tocography in all 28 women; FBM were present on admission in 11 and absent in the remaining 17. No significant differences were found in maternal age and gestational age between the two groups (Table 1). Five women had a Bishop score of >5 and FBM were absent in all five (Table 1).

The prognostic value of the presence or absence of FBM on admission was assessed in terms of termination of pregnancy within 1 week of admission (Table 2). None of the 11 women with demonstrable FBM was delivered during this period and the contractions subsided spontaneously. Of the 17 patients admitted with uterine contractions but no detectable FBM, eight responded to tocolytic treatment. Further scans after 72 h revealed the reappearance of FBM. The other nine patients proceeded to delivery within 1 week despite tocolysis, five of them within 48 h.

Discussion

Castle & Turnbull (1983) were the first to demonstrate that the presence or absence of FBM can help to predict the outcome of premature onset of labour. In the present study about 40% of the patients who presented with premature contractions continued the pregnancy without any treatment and in all of them FBM were present. Moreover, eight women in whom FBM were absent on admission demonstrated FBM after 72 h of successful tocolytic treatment. In all these patients pregnancy continued, showing again the predictive value of FBM. Furthermore, this fact demonstrated the efficacy of tocolytic therapy in patients with premature labour in the absence of FBM.

Tocolytic agents may cause severe side-effects. (Pritchard *et al.* 1985). In all 11 of the 28 patients (39%) in this study, FBM were present so that unnecessary tocolytic therapy was not given,and possible side-effects were avoided in these patients.

Table 2. Correlation between the Bishop score on admission fetal breathing movements (FBM) and the outcome of preterm labour

	Bishop score on admission		
	≤5	>5	Total
FBM present (*n* = 11)			
Admission to delivery interval			
≥1 week	11	—	11
<1 week	0	—	—
FBM absent (*n* = 17)			
Admission to delivery interval			
≥1 week	8†	—	8
<1 week	4(1*)	5(4*)	9(5*)

* Delivered within 48 h.

† FBM present after 3 days.

The decrease in fetal breathing activity which occurs during labour (Boddy & Dawes 1975; Boylan & Lewis 1980) is in some way related to an increase in uterine activity or to the progress of labour (Richardson *et al.* 1979), although no connection was demonstrated between the inhibition of fetal breathing and oxytocin administration, epidural analgesia or ruptured membranes (Richardson *et al.* 1979). The link between labour and FBM may be fetal prostaglandin E_2 (PGE_2) (Castle & Turnbull 1983) which was found to increase during labour (Bibby *et al.* 1979). As well as stimulating uterine contractility, PGE_2 can inhibit fetal breathing in laboratory animals (Koobs 1982). Moreover, the reappearance of fetal breathing after contractions are inhibited with tocolytic therapy may suggest a possible link between the presence of local PG and the relaxant effect of betamimetics on the uterus.

The predictive value of FBM should increase the objectivity in diagnosis of preterm labour and diminish the unnecessary use of tocolytic therapy.

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Routine hysteroscopy for patients with a high risk of uterine malignancy

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Summary. Seventy patients with abnormal vaginal bleeding were examined with a Storz hysteroscope. The examination took an average of only 5 min. Sixty patients had the examination under general anaesthesia, five under paracervical block and five had no form of anaesthesia. All tolerated the procedure well. There were no complications directly related to the hysteroscopic examination. There was complete correlation between the histology of the endometrium obtained at subsequent curettage and the hysteroscopic findings.

Diagnostic endoscopy with its facility for direct viewing has superseded most indirect diagnostic procedures in every branch of medicine. The laparoscope has revolutionized the diagnosis of intra-abdominal pathology in gynaecological practice. The use of the hysteroscope to investigate intrauterine pathology has been studied by several investigators but there seems to be a hesitancy to adopt this most useful endoscopic examination (in every day gynaecological practice) as a routine diagnostic procedure in place of dilatation and curettage (D & C). In the present study we performed routine hysteroscopic examination in consecutive patients with a high risk of uterine malignancy, in whom a diagnostic D & C was clinically indicated.

Patients and methods

From March 1984 to October 1985 70 patients had a hysteroscopic examination before diagnostic curettage, 49 were postmenopausal, 18 perimenopausal and three were premenopausal. The age range was between 28 and 85 years (mean 56 years).

Of the 70 patients, 60 had the hysteroscopy under general anaesthesia, five had a paracervical block with 1% lignocaine and the remaining five had no form of anaesthesia. Informed, written consent was obtained from all the patients before the operation.

Instruments

A Storz microhysteroscope of 4 mm diameter with an outer sheath of 5·2 mm diameter and a channel to allow insufflation with carbon dixoide from a hysterosufflator via rubber tubing was used. A gas flow rate of 30 ml/min was maintained and an automatic fall in the flow rate occurred when the intrauterine pressure reached 90 mmHg. A standard fibreoptic light source was used.

No cervical dilatation was required in 65 patients before the introduction of the hysteroscope, unless an operating sheath with a diameter of 7 mm was used to obtain biopsies. Five patients required initial dilatation of the cervix to 5 Hegar. In common with other investigators (Taylor & Hamou 1983; Lindemann & Mohr 1976) we did not use a cervical cup to provide a gas-tight seal at the cervix. We did not consider vaginal bleeding at the time of the operation as a contraindication to hysteroscopy. A majority of our patients were postmenopausal and vaginal

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bleeding at the time of hysteroscopy was not profuse.

The patients were put in the dorsal lithotomy position, the vulva and vagina were cleaned with an antiseptic solution and the patient draped. A bimanual examination was performed to determine the size, mobility and position of the uterus. The cervix was exposed with a speculum. A paracervical block, using 1% lignocaine, was injected in five patients who had no general anaesthesia. The cervix was then grasped with a tenaculum. The assembled Storz hysteroscope was introduced into the external cervical os and the gradual inflow of carbon dioxide gas commenced. This created a chamber of gas in the endocervix which gently dilated the internal cervical os and facilitated the introduction of the distal end of the hysteroscope into the uterine cavity. The endocervix uterine fundus, anterior and posterior uterine walls and the tubal ostia were examined systematically. Once the examination was complete the hysteroscope was withdrawn. A biopsy of any intrauterine lesion was usually taken under direct vision after reintroducing the hysteroscope with the operating sheath. This generally required the dilatation of the cervix to 7 mm. Alternatively the biopsy was taken by directing a polyp forceps or a fine curette towards the site of the lesion as determined by the hysteroscopy. The specimens obtained were sent for histological examination. the biopsies that were obtained through the hysteroscope were adequate for histological interpretation. The hysteroscopic examination took on average only 5 min. All the patients had curettage immediately after the hysteroscopic examination was completed.

Results

Of the 49 patients who presented with postmenopausal bleeding 11 had endometrial carcinoma and there was one Stage II cervical carcinoma. Six had atrophic endometrium; 17 had no endometrium but seven of them had isolated intrauterine polyps of which five were benign, one showed adenomatous hyperplasia and one cystic hyperplasia. In the remaining 14 patients, five had cystic hyperplasia of the endometrium, two had proliferative endometrium, three showed signs of endometritis, three had small submucosal fibroids and one pyometra was diagnosed on hysteroscopic examination.

Five women were having hormone replacement therapy and had irregular vaginal bleeding. Three of them had cystic hyperplasia and two had secretory phase endometrium. Two patients who were receiving long-term tamoxifen therapy for carcinoma of the breast had had postmenopausal bleeding and hysteroscopy showed adenomatous hyperplasia in one and polyp with cystic hyperplasia in the other.

Eleven patients had hysteroscopic examination for perimenopausal bleeding. Two had submucosal fibroids; three had signs of endometritis; five showed proliferative endometrium and one patient had adenomatous hyperplasia.

Three patients aged 28, 42 and 52 years had persistent menorrhagia. On hysteroscopic examination the 42-year-old had an exophytic, well differentiated adenocarcinoma of the endometrium, the 52-year-old patient had a single endocervical polyp which was removed during the examination; histologically this was well-differentiated adenocarcinoma but, after hysterectomy, the uterus contained no residual tumour. In this patient hysteroscopy enabled a diagnosis of endocervical adenocarcinoma to be made and definitive treatment was planned accordingly. The third patient was a 28-year-old woman who was referred from another hospital where she had had a diagnostic curettage for persistent menorrhagia and anaemia. Uterine curettings, although macroscopically normal, had contained two fragments of papillary adenocarcinoma. In view of the patient's age and the low probability of endometrial carcinoma in this age group, the gynaecologist had repeated the D & C twice at 2-monthly intervals and on both occasions had obtained only benign endometrium; a hysteroscopic examination elsewhere had revealed no endometrial malignancy. As the patient continued to have heavy irregular bleeding she was referred to St Thomas's Hospital for further hysteroscopic examination. She had clearly defined tumour at the uterine fundus.

In two patients, one with adenocarcinoma of the endocervix and the other with squamous cell carcinoma of the cervix, the hysteroscope was used to delineate the extent of the tumour for staging of the disease before definitive treatment.

There were no discrepancies between the diagnoses derived from the hysteroscopic biopsies and that from the endometrium removed at subsequent curettage.

All the patients tolerated the procedure well.

Of the five patients who had no form of anaesthesia only two complained of 'period-like' pain and three of the five patients who had paracervical block complained of a similar pain at the time of the biopsy. Of the patients who had the procedure under general anaesthesia 20% had some pelvic discomfort afterwards. None of the patients required postoperative analgesia. The one patient who had a pyometra was treated with antibiotics. There were no instances of postoperative pelvic infection. The patients who had malignant disease diagnosed at hysteroscopy had peritoneal washings taken for cytological examination, at subsequent hysterectomy operation and no malignant cells were detected in any of the 15 who had surgical treatment. There were no uterine perforations or episodes of abnormal vaginal bleeding following hysteroscopy.

Discussion

Word *et al.* (1958) showed that 10% of endometrial lesions may be missed by traditional D & C since a D & C is a blind procedure. Stock & Kanbour (1975) reported 50 patients in whom a hysterectomy specimen was examined after a pre-operative D & C, in 60% of them only half the uterine cavity had been curetted. In our study there were no false negative results at hysteroscopic examination.

Hysteroscopy is valuable in the diagnosis and location of solitary lesions of malignant potential or of malignancies. Our 28-year-old patient with persistent menorrhagia associated with an adenocarcinoma of the endometrium illustrates the value of a direct viewing of the uterine cavity over a blind technique. Unfortunately no one has investigated how often solitary intrauterine lesions are missed during routine D & C but the possibility is a cause for concern.

Another popular procedure used as an alternative to D & C for obtaining samples of endometrium for histologic examination is Vabra aspiration. Grimes (1982) reviewed the published comparisons of D & C and Vabra aspiration and reported that Vabra aspiration detected 96% of adenocarcinoma and 80% benign polyps. Vabra aspiration is often used to supervise women receiving hormone replacement therapy but it is likely that this is less efficient than hysteroscopic examination.

The choice of a diagnostic procedure should be based on diagnostic accuracy, patient acceptability and the cost. The modern hysteroscope is superior in all of these respects to the long-established procedures used to investigate patients at high risk for uterine malignancy. The use of the hysteroscope on conscious out-patients either with paracervical block or without anaesthsia, may provide a reliable technique for screening women for endometrial carcinoma.

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The night—a dangerous time to be born?

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Summary. An analysis of perinatal mortality by hour of birth among 10 059 births in Canton Ticino (Switzerland) during the years 1979–1982 showed that fewer births occurred at night than during the day. The variations in number of births by hour of birth were attributed to obstetric practices. The perinatal mortality rate for night-time births was more than twice as high as that for the daytime births (+127%, $P<0\cdot001$) and the rates for night-time births exceeded those for daytime births for 13 of the 19 causes of death examined. A higher proportion of the low and very-low-birthweight babies (<2500 g and <1500 g) were born at night between 19.00 and 06.59 hours.

The weekend, particularly Sunday, has been recognized as a dangerous period for births. Perinatal mortality at these times has been found to be higher than on weekdays in England and Wales (Macfarlane 1978; Hendry 1981), Arkansas (Mangold 1981), Australia (Mathers 1983) and Switzerland (Federal Office of Statistics 1984; Paccaud *et al.* 1984). The present study investigated the hypothesis that, if hospital night-time conditions are similar to those during weekends [fewer deliveries than in the daytime (Federal Office of Statistics 1984) reduced levels of staff and medical care (Tyson *et al.* 1981) and a possible concentration of non-inducible high-risk births (Mathers 1983)] then it is likely that nocturnal patterns of higher perinatal mortality rates would be similar to those found during weekends.

Subjects and methods

In Switzerland each Canton, as an independent Republic, has the primary and main responsibility for public health in general, and hospital administration in particular. For this reason, every year each Canton receives a copy of its own part of the central file record from the Federal Office of Statistics where all data concerning official birth and death certificates are collected.

This study is an analysis of the variation in perinatal mortality rates by hour of birth among the 10 059 births (including stillbirths) in the Canton Ticino (the Italian speaking part of Switzerland) during the years 1979–1982. Swiss birth certificates note the hour of live birth and stillbirth as well as the birthweight.

Death certificates also indicate the hour of birth for each infant dying within 27 days of birth and, in particular, the cause of death according to the International Classification of Disease (ICD) 8th revision.

Births recorded as having occurred in hospital (in all seven obstetrical departments and units of Canton Ticino) accounted for 99·4% of the total births during 1979–1982. No perinatal death was identified when delivery occurred at home. Central to this analysis is the assumption that perinatal mortality is independent of the hour of birth but depends on the number of births in each time period under analysis.

The main results of this study were discussed with a group of obstetricians and paediatricians working in the departments and units analysed. The probability level was calculated by χ^2 test.

Results

Births

Table 1 shows the observed number of births (including stillbirths) recorded for each 6-h

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Table 1. Number of births and perinatal mortality rate recorded for each 6-h period of the day and expressed as percentages of the average expected number and rate (observed/expected ratio) among the 10 059 births in Canton Ticino (Switzerland) during the years 1979–1982

	Number of births		Perinatal mortality	
Time of birth	Observed no.	Observed/expected ratio	Observed rate	Observed/expected ratio
Night-time (hours)				
19.00–00.59	1719	68	19·8	167
01.00–06 59	1925	77	17·1	145
19.00–06.59	3644	72	18·4	156
Daytime (hours)				
07.00–12.59	3698	147	7·6	64
13.00–18.59	2717	108	8·8	74
07.00–18.59	6415	128	8·11*	68
Total	10 059		11·8	

*Significance of difference between rates for day and night-time births $P<0{\cdot}001$.

period of the day and expressed as a percentage of the average expected number of births (observed/expected ratio) among the 10 059 births in Canton Ticino during the years 1979–1982. Figure 1 illustrates the variation in the observed/expected ratio by hour of birth during the 24 h day; the ratio reaches its highest value between 08.00 and 10.00 hours. The 12 daytime hours (07.00–18.59 hours) account for 64% of the births in the whole 24 h.

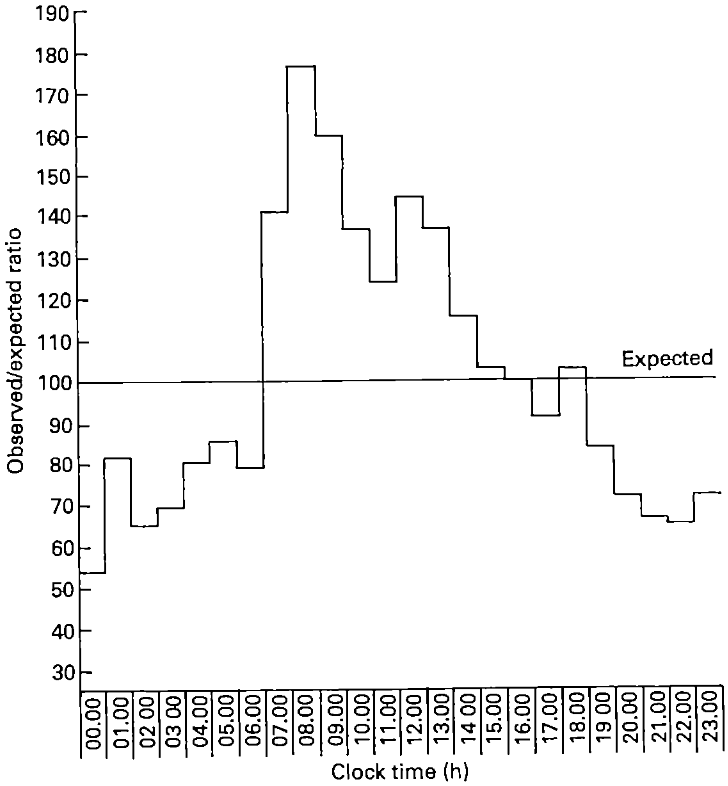

Fig. 1. Ratio of the observed/expected number of births for each hour of the day among 10 059 births in Canton Ticino (Switzerland) during the years 1979–1982

Perinatal mortality

Table 1 also shows the perinatal mortality rates (stillbirths and deaths during the first 7 days of life) recorded for each 6-h period of the 24-h day among the 10 059 births in the study group, and the ratios of the observed to the expected perinatal mortality rates. The difference in the perinatal mortality rates between the daytime and night-time was striking with the night-time rate more than twice as high (+127%, $P<0{\cdot}001$). As demonstrated previously for weekend births (MacFarlane 1978; Hendry 1981; Mangold 1981) an inverse relation ($r = 0{\cdot}93$) was found for night-time births in which lower numbers of deliveries were associated with higher perinatal mortality rates.

Since birthweight is by far the most important factor associated with perinatal mortality, we examined the distribution of birthweights during the 24th day and the observed/expected ratios (adjusted for the number of births), detailed in Table 2, showed that a higher proportion of the low birthweight babies (<2500 g) were born at night between 19.00 and 06.59 hours (Table 2). The difference was most striking for the very-low-birthweight babies (<1500 g). The highest proportion of the low-birthweight babies (<2500 g) were born between 19.00 and midnight.

A further analysis (Table 3) of the deaths occurring in the first 2 h of life showed that the mortality rate for the nocturnal births was more than three times as high (+227%) as the rate for daytime births ($P<0{\cdot}001$).

Table 4 illustrates the distribution of all causes of perinatal deaths between night- and day-time births. For 13 of the 19 causes the nocturnal births had higher mortality rates. For five causes the excess nocturnal mortality rate was statistically significant (from $P<0{\cdot}06$ to $P<0{\cdot}001$). Several causes of death were present only in night-time births.

Discussion

Quality of the data

Data about the hour of birth of the 119 perinatal deaths (stillbirths and first week deaths), obtained from the central file record of official certificates, were verified through hospital regis-

Table 2. Ratio of the observed/expected number of births in three birthweight categories according to hour of birth in Canton Ticino (Switzerland, 1979–1982)*

Time of birth	Observed/expected ratio in three birthweight groups <1550 g	 1550–2499 g	 ≥2550 g
Night-time (hours)			
19.00–00.59	171	121	98
01.00–06.59	141	102	100
19.00–06.59	155	111	99
Daytime (hours)			
07.00–12.59	65	89	101
13.00–18.59	73	101	100
07.00–18.59	69	94	101

*Babies with unknown birthweight are excluded; they represented 0·24% of the total births and showed no relation to the hour of birth.

Table 3. Mortality rates and ratios of observed/expected rates in the first 2 h of life according to time of birth among 10 002 live births in Canton Ticino (Switzerland) during the years 1979–1982

Time of birth	Mortality rate/1000 live births Observed	 Observed/expected ratio
Night-time (hours)		
19 00–06.59	3·6*	181
Daytime (hours)		
07.00–18.59	1·1*	55

*Significantly different $P<0{\cdot}01$.

Table 4. Perinatal mortality rates according to causes of death (ICD 8th revision) and by time of birth among the 10 059 births in the Canton Ticino (Switzerland) during the years 1979–1982

Cause of death*	Perinatal mortality rate			Significance of difference P†	Night-time excess
		Time of birth			
	Total	Night-time (19.00–06.59 h)	Daytime (07.00–18.59 h)		
Stillbirths	5·7	8·23	4·21	<0·01	+
Perinatal causes (760–779)	4·1	7·41	2·18	<0·001	+
Anoxia, hypoxia (776)	2·1	3·57	1·25	<0·02	+
Immaturity (777)	0·7	1·65	0·16	<0·01	+
Other conditions (778)	0·5	0·82	0·31	NS	+
Conditions of placenta (770)	0·2	0·55	—	<0·06	+
Haemolytic disease (775)	0·2	0·55	—	<0·06	+
Toxaemia of pregnancy (762)	0·1	0·28	—	NS	+
Other complications (769)	0·1	—	0·16	NS	–
Maternal infection (763)	0·1	—	0·16	NS	–
Fetal death (unknown) (779)	0·1	—	0·16	NS	–
Congenital anomalies (740–759)	1·7	2·20	1·40	NS	+
Heart (746)	0·5	0·55	0·47	NS	+
Musculo skeletal systems (756)	0·3	0·55	0·16	NS	+
Affecting multiple systems (759)	0·3	0·55	0·16	NS	+
Urinary systems (753)	0·1	0·28	—	NS	+
Anencephalus (740)	0·3	0·28	0·31	NS	–
Respiratory system (748)	0·2	—	0·31	NS	–
Infectious (000–136)	0·3	0·28	0·31	NS	–
Diarrhoeal disease (9)	0·1	—	0·16	NS	–
Septicaemia (38)	0·2	0·28	0·16	NS	+
Respiratory system (460–519)	0·01	0·28	—	NS	+
Pneumonia (486)	0·01	0·28	—	NS	+
Total	11·8	18·4	8·11	<0·001	+

*According to the International classification of Disease 8th revision. †χ^2 test.

ters of births and deaths. In three cases there was a discrepancy in the records about the hour of birth but this did not affect the results once the hours of birth were grouped into 6-h periods. It might also be possible that a mistake was made in the original registration of the hour of birth. Here too the grouping procedure particularly the division into two groups, night and day, has reduced the risk of errors having influenced the main results of this study.

It is very unlikely that the birthweights recorded on birth certificates are strongly biased by the hour of birth. Furthermore, the proportion of unknown birthweight is very low in Switzerland (Federal Office of Statistics 1985); in Canton Ticino this proportion (0·24%) was unrelated to the hour of birth.

Reported causes of deaths have not been verified from the clinical histories, but the causes are only those registered by doctors (obstetricians and paediatricians). No autopsy data were available.

Time of birth

Variation in number of births according to the hour of day has been reported from Switzerland (Federal Office of Statistics 1984) where daytime hours, in particular the morning, account for more live births than night time. There is little doubt that the variation in number of deliveries by hour of birth is a reflection of obstetric practice but unfortunately there are no data on the timing of obstetric intervention such as the induction of labour and caesarean section. In 1982, in Canton Ticino, 18·4% of all deliveries were by caesarean section (varying between 12·7 and 33% in the different departments and units). The obstetricians and paediatricians who participated in the discussion of our results stated that the highest value of the observed/expected number of births ratio, found between 08.00 and 10.00 hours, was a consequence of the high concentration of elective caesarean sections at that time and the relatively high ratios between noon and 13.00 hours reflected the effect of induction of labour, which usually started between 07.00 and 08.00 hours.

Perinatal mortality

The variations in perinatal mortality rates by hour of day (Table 1) must be discussed in the context of the higher mortality rates observed during the weekend in Switzerland (Federal Office of Statistics 1984) and in Ticino (Domenighetti 1985). Although the nocturnal excess perinatal mortality (+ 127%) is much greater than that for Sundays (+ 45%), this common pattern might suggest a common set of causes. This pattern is similar to that found for the proportion of low-birthweight babies (<2500 g), which was higher during night-time (Table 2) and during the weekends, in Switzerland, for the years 1979–1981 (Federal Office of Statistics 1985).

This pattern could be attributable to the concentration during these times of non-inducible high risk births, as already mentioned by MacFarlane (1978). An alternative explanation could be the lower staff level available leading to a poorer level of obstetric and neonatal care. This analysis cannot offer definitive support for these possibilities. The fact that there are more low-birthweight babies born at night might suggest a selection process (i.e. concentration of high risk babies); it might also be attributable to a lower level of obstetric care during the night, leading to an higher rate of preterm delivery (Korenbrot *et al.* 1984).

However, the shift towards low- and very-low-birthweight babies during the night does not explain entirely the observed excess mortality; this can be indirectly assessed using Table 2 and birthweight-specific mortality rates published elsewhere (Federal Office of Statistics 1985). Direct analysis shows that perinatal mortality rates are higher during the late afternoon and evening in each birthweight group (F. Paccaud, unpublished observations) indicating that neonatal care is a possible contributory factor, the striking excess mortality observed during the first 2 h of life might be taken as further support.

Whatever the causes of this pattern the present analysis shows that there are short-term variations in perinatal mortality rates that are probably attributable to a service effect and that at least part of the excess night mortality could be attributed to the reduced staff level available at this time. Tyson *et al.* (1981), in a 23-day analysis of newborn intensive care by time-lapse photography, reported that activities of physicians were significantly diminished at night and at weekends. The deterioration in the performance at night was associated with an increase in neonatal acidosis and mortality. Obstetricians and paediatricians who participated in the final discussion of the results noted the difficulties in organizing urgent caesarean sections during the night, and in having staff on call particularly for anaesthesia, respiratory resuscitation and blood transfusion.

Further insight in those topics should be provided by careful clinical studies as substantial improvements in perinatal mortality could result from such an effort.

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Fetal transcutaneous carbon dioxide monitoring — the effect of different fixation methods

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Summary. Fetal transcutaneous carbon dioxide tension (tc-$P\text{CO}_2$) was monitored simultaneously by two electrodes fixed with glue or suction during 10 deliveries. There were no differences in success rate, tc-$P\text{CO}_2$ readings or stabilization time between the two fixation methods, but the glue fixation method was more time consuming, caused more discomfort to the patient and generally did not permit reapplication of the electrode.

Monitoring of fetal transcutaneous carbon dioxide tension (tc-$P\text{CO}_2$) during labour, investigated during the last 3 years (Nickelsen *et al.* 1985; Thomsen & Weber 1984; Hansen *et al.* 1984; Schmidt *et al.* 1984), has shown close correlations between tc-$P\text{CO}_2$ and $P\text{CO}_2$ values measured in both capillary and umbilical artery blood. Two different techniques for application of the electrode are in current use, but there are no published studies that compare the glue and suction fixation methods. This study was designed to investigate the two methods of electrode fixation by using both simultaneously in the same patient and comparing the reliability, success rate and stabilization time.

Subjects and methods

Ten women in labour, nine at term and one at 33 weeks gestation, participated in the study after giving informed consent. No high-risk patient was included in the study, and the women were selected from consecutive deliveries, where an investigator was present to monitor tc-$P\text{CO}_2$.

After calibration with 5% and 10% CO_2/N_2 gas, two tc-$P\text{CO}_2$ electrodes (Radiometer E5230) were sterilized in a 3% solution of aldehydes (Korsolin, Ferrosan, Copenhagen) for 20 min. The electrodes were connected to two CO_2 monitors (Radiometer TCM220) and the readings were recorded in one curve. A measuring temperature of 44°C was used.

Glue fixation method

The electrode was mounted in a sterilized glue fixation ring, similar to those used in neonatal monitoring, but after removal of the adhesive tape. A special application tool was used to hold the electrode during application (Fig. 1). Just before application 2-butylcyanoacrylat (Histoacryl, B. Braun, Melsungen FRG) glue was applied to the fixation ring. The electrode was kept vertical until immediately before electrode application to prevent the glue from flowing off the ring or into the electrode membrane.

After rupture of the membranes and a cervical dilatation of at least 4 cm, the leading part of the fetal head was seen with a 33 mm amnioscope. The skin was cleaned with cotton swabs, but as all fetuses had sparse hair this was not shaved or cut. The electrode in the glue fixation ring was firmly pressed against the fetal head for 1 min before the application tool and the amnioscope was removed.

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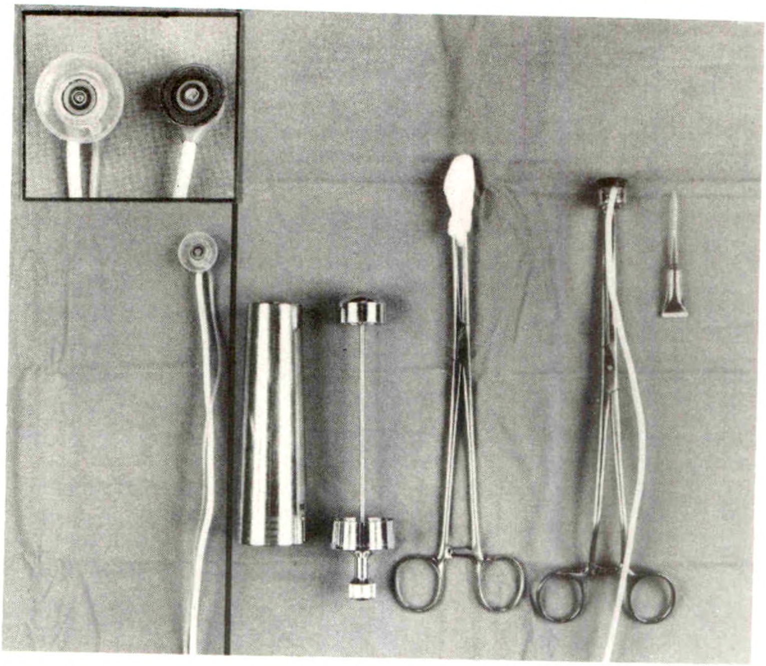

Fig. 1. *Left:* transcutaneous carbon dioxide electrode mounted with suction fixation ring. *Right:* transcutaneous carbon dioxide electrode mounted with glue fixation ring in the application tool. Amnioscope, cotton swabs and the glue ampoule are necessary for application. *Inset:* Close-up of the electrodes and fixation rings.

Suction fixation method

The electrode was mounted in the sterilized suction ring (Fig. 1). No application tool or amnioscopy were necessary for this method. Just after the first electrode was fixed on with glue, the amnioscope was removed and vaginal examination was performed. The electrode in the suction ring was held between two fingers and pressed against the fetal head as near to the other electrode as possible. An electrical pump supplied the suction ring with a negative pressure of 20 kPa (150 mmHg). After application of the electrodes, the stabilization time (i.e. the time from application until 95% of the stable value was achieved) was measured for both electrodes. The simultaneous tc-$P\text{CO}_2$ readings of the two electrodes were recorded just after application, just before delivery (or just before end of monitoring) and after approximately 50% of the monitoring time.

The distance from the centre of the glue-fixed electrode (applied in the centre of the cervical os) to the farthest edge of the suction-fixed electrode was almost 4 cm when the two electrodes were placed as close as possible to each other. At a cervical dilatation of $\geqslant$ 8 cm (>4 cm from centre to cervical edge) both electrodes were usually free of compression from the cervical edge, and therefore the tc-$P\text{CO}_2$ values at cervical dilatations of $\geqslant$ 8 cm were analysed separately to eliminate any effects of interference by electrode compression.

After monitoring both electrodes were examined for drift by the 5% CO_2 gas.

Table 1. Stabilization time for electrodes fixed with glue or suction

Electrode fixation method	*n*	Stabilization time (min)		
		Median	Interquartile range	Range
Glue	9	6·6	3·8–8·4	1·5–17
Suction	9	6·6	5·2–9·2	1·5–10·8

Table 2. Simultaneous transcutaneous CO_2 tension (tc-$P\mathrm{co}_2$) measurements using two electrodes applied with glue or suction fixation

		tc-$P\mathrm{co}_2$ (kPa)			
Cervical dilatation	*n*	Glue fixation	Suction fixation	Difference*	*t**
<8 cm	11	9·4 (1·2)	8·6 (1·0)	0·8 (0·6)	2·46 $P<0{\cdot}05$
≥8 cm	14	9·7 (2·2)	9·7 (2·4)	0·0 (0·6)	−0·39
Total	25	9·5 (1·8)	9·2 (1·9)	0·3 (0·9)	1·73

Results are mean (SD) values.

* Mean of the differences between paired simultaneous measurements from the glue- and suction-fixed electrodes (two-tailed paired *t*-test).

Statistics

Differences in mean values of tc-$P\mathrm{co}_2$ obtained by the two fixation methods were evaluated by a two-tailed paired *t*-test (significance level $P<0{\cdot}05$). Differences in stabilization times were evaluated by Wilcoxon's signed rank test (significance level $P<0{\cdot}05$).

Results

Monitoring until delivery was successful with the glue-fixed electrode in six patients, the electrode fell off during the second stage in three patients and was removed in one patient at a cervical dilatation of 7 cm when she had a caesarean section. Monitoring with the suction-fixed electrode also succeeded in six patients, although the electrode was re-applied in one patient during the second stage. In three patients the electrode fell off during the second stage of labour and was not re-applied and in the patient delivered by caesarean section the electrode was removed together with the glue-fixed electrode. Stabilization times were similar for the glue- and suction-fixed electrodes (Table 1).

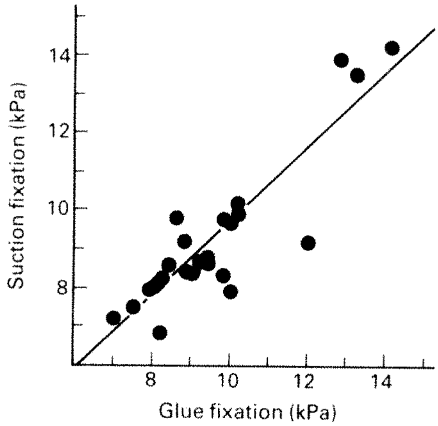

Fig. 2. Correlation between simultaneous tc-$P\mathrm{co}_2$ values measured by glue- and suction-fixed electrodes in all patients. $y=0{\cdot}97x + 0{\cdot}02$; $r=0{\cdot}89$; $n=25$; $P<0{\cdot}001$.

In five patients monitoring time was short and only the tc-$P\mathrm{co}_2$ values from the start of monitoring and those just before the end of monitoring were available, so that 25 simultaneous values obtained from the glue- and suction-fixed electrodes and analysed. The mean (SD) tc-$P\mathrm{co}_2$ values are shown in Table 2 together with the mean value of the differences between simultaneous readings. The only statistically significant difference was found between measurements at a cervical dilatation of <8 cm.

The correlations between measurements from the glue- and suction-fixed electrodes are shown in Figs 2 and 3, demonstrating a closer correlation at a cervical dilatation of ≥8 cm.

Discussion

Suction fixation of electrodes was our usual method for tc-$P\mathrm{co}_2$ monitoring before this study. The glue fixation method was learned during 10 deliveries before the study, and this short period of training was sufficient to obtain a success rate equivalent to that obtained with suction fixation. Nevertheless, glue fixation was more time consuming and caused more discomfort to the patient, as it involved a dorsal position and amnioscopy. Reapplication of the glue-fixed electrode was not attempted in this study as it

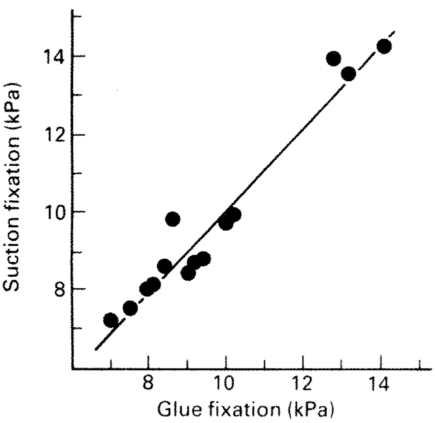

Fig. 3. Correlation between simultaneous tc-Pco_2 values measured by glue- and suction-fixed electrodes in patients with cervical dilatation ≥ 8 cm. $y=1{\cdot}05x - 0{\cdot}47$; $r=0{\cdot}97$; $n=14$; $P<0{\cdot}001$.

could involve changing the electrode membrane, recalibration and resterilization because of glue contamination of the electrode membrane. In contrast, reapplication of the suction-fixed electrode is simple and involves no change of membrane or recalibration.

The methods for applying monitoring electrodes have been investigated previously (Löfgren 1978; Huch *et al.* 1977; Weber & Secher 1979) in comparative studies between two series of tc-Po_2 monitoring using electrodes fixed either with glue or suction but the two methods gave similar values.

In the present study, the simultaneous readings of two tc-Pco_2 electrodes fixed with glue or suction showed a close correlation, especially at cervical dilatations of ≥ 8 cm. At lesser dilatations one of the electrodes could be subjected to compression by the cervical edge which could affect the tc-Pco_2 reading (Nickelsen & Weber 1986).

Figures 2 and 3 show three tc-Pco_2 values of >13 kPa (at 44°C), they were measured in the same fetus at cervical dilatations of between 8 and 10 cm. The baby had a 1-min Apgar score of 9, an umbilical artery blood pH of 7·12 and a Pco_2 of 14·0 kPa (at 44°C) indicating respiratory acidosis. Stabilization times did not differ between the glue- and suction-fixed electrodes but they were longer than in previous studies that used suction fixation. Usually the natural humidity of the fetal skin in the birth canal serves as contact liquid (with a Pco_2 in equilibrium with tc-Pco_2) when suction fixation is used, but in the present study no liquid was left after the skin was cleaned and dried. This may explain the longer stabilization times found in this study.

The exclusion of differences in mean values is invalidated by the low number of measurements. A difference of 0·6 kPa (SD of the difference) is excluded (90% statistical power) when 14 measurements are analysed. This means that a larger series might expose a difference of <0·6 kPa, although close correlations were found in this study.

We conclude that the suction fixation method is simple and less time consuming than the glue fixation method. Values obtained with the two fixation techniques are very similar and any differences are not important clinically.

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The effect of electrode compression during fetal transcutaneous carbon dioxide monitoring

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Summary. The influence of electrode compression by the cervix on transcutaneous CO_2 measurements (tc-Pco$_2$) was studied during 20 deliveries by simultaneous measurements with two electrodes, one positioned under the cervical edge and the other free of the cervix. At a cervical dilatation of <8 cm, significantly higher values were measured by the electrode exposed to cervical compression, and tc-Pco$_2$ fluctuations with uterine contractions were observed. This study confirms that the tonsure effect usually does not interfere with tc-Pco$_2$ monitoring.

Compression of the electrodes used for transcutaneous monitoring may theoretically compromise the capillary blood flow in the skin beneath the electrode. Studies on adult volunteers have demonstrated that a weight of 30–110 g on a tc-Po$_2$ electrode placed on the scalp, may reduce capillary blood flow and cause tc-Po$_2$ values of zero (O'Connor *et al.* 1979). Although the diffusion of carbon dioxide through the skin is easier, these problems also affect tc-Pco$_2$ monitoring. To demonstrate this, a calibrated tc-Pco$_2$ electrode was placed on the scalp of a day-old healthy mature baby with an ordinary fixation ring (with adhesive tape) and with contact liquid between the membrane and the skin. After stabilization of the tc-Pco$_2$ value a weight of 100 g was applied to the electrode for 6 min. A distinct increase of tc-Pco$_2$ appeared 2 min after the weight was applied (Fig. 1). Removal of the weight from the electrode induced an immediate decrease in tc-Pco$_2$ and 2 min later tc-Pco$_2$ was stabilized at a level 0·2 kPa above the initial value.

During fetal monitoring, compression of the electrode may occur between the fetal head and the lower segment of uterus. This study evaluates the effect of this compression by simultaneous monitoring with two electrodes, the one placed between the fetal head and the cervix, the other in the centre of the cervical os.

Subjects and methods

After giving informed consent 20 women in labour at term were included in the study. No high-risk patient was included, and consecutive deliveries, where tc-Pco$_2$ monitoring was possible (investigator present during labour and delivery) were selected for the study. After sterilization and calibration (Nickelsen & Weber 1986) two tc-Pco$_2$ electrodes (Radiometer E5230) were mounted in suction fixation rings. The first electrode was applied in a lateral position between the cervix and the fetal head. The second electrode was applied in the centre of the cervical os, without compression from the cervical edge (Fig. 2). The readings were recorded simultaneously on the same curve, and by frequent vaginal examinations the cervical dilatation and the readings of both electrodes were recorded. After each monitoring electrode drift was assessed. An electrode temperature of 44°C was used.

Statistics

Differences in mean values of tc-Pco$_2$ measured

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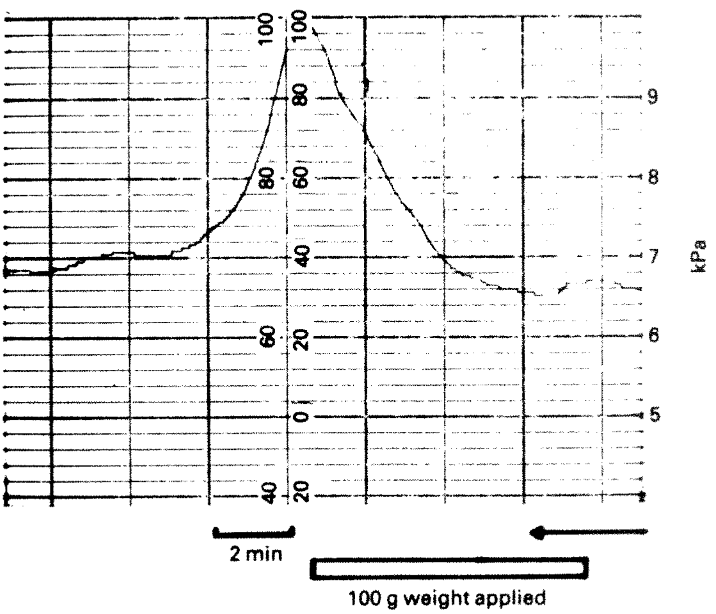

Fig. 1. Effect of electrode compression during neonatal tc-$P\text{co}_2$ monitoring. The tc-$P\text{co}_2$ increase is delayed approximately 2 min, but the decrease happens immediately after cessation of compression.

by the electrodes positioned centrally and laterally were evaluated by a paired *t*-test.

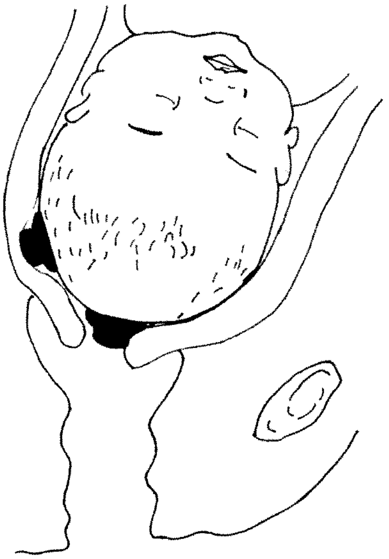

Fig. 2. tc-$P\text{co}_2$ electrodes applied in lateral position (to the left) between the cervix and the fetal head and in central position free of compression from cervix.

Results

During monitoring the central electrode usually showed stable values in contrast to the lateral electrode which fluctuated in relation to uterine contractions, with increasing tc-$P\text{co}_2$ values during the last part of the contraction, maximum just after, and decreasing values in the first period between contractions (Fig. 3). These fluctuations often disappeared at a cervical dilatation of ≥8 cm, when the lateral electrode was usually free of the cervical edge and not compressed. During 20 deliveries simultaneous readings of the central and lateral electrode were noted in relation to vaginal examination on 76 occasions. Mean values calculated for both electrodes and the difference between simultaneous readings are listed in Table 1. The lateral electrode reading was significantly higher than the central one, but no significant difference was found at a cervical dilatation of ≥8 cm. During the first stage of labour the highest value was measured usually by the lateral electrode, but during the second stage of labour, when the fetal head was pressed against the pelvic floor, the highest value in some cases was measured by the central electrode.

The median (25–75 centile) values of stabilization times of the central and lateral electrode

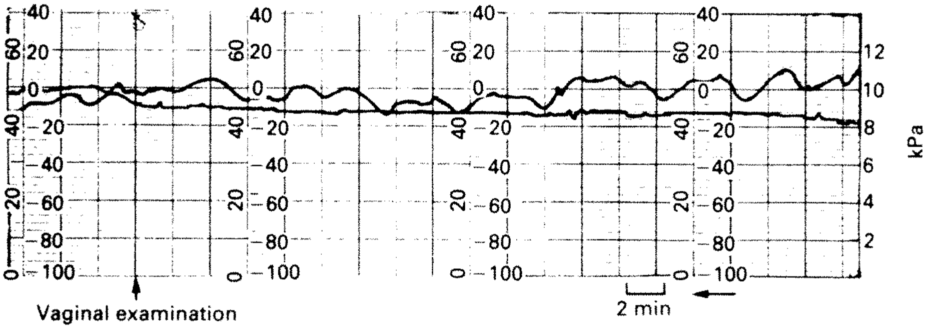

Fig. 3. tc-$P\mathrm{CO}_2$ monitoring with electrodes in lateral and central position. At the start (to the right) the lateral electrode reading is higher than the central electrode reading and shows fluctuations according to uterine contractions. Following vaginal examination the compression of the lateral electrode is revealed and the reading decreases to values just below the central electrode reading.

were 2·4 (2·0–3·2) min and 2·5 (2·0–3·8) min, respectively.

Discussion

Low tc-$P\mathrm{O}_2$ values caused by compromised capillary blood flow by compression of the transcutaneous electrode have been described previously (O'Connor *et al.* 1979). Increasing tc-$P\mathrm{CO}_2$ values due to similar electrode compression were demonstrated during neonatal monitoring. Aerobic metabolism with formation of carbon dioxide only continues as long as oxygen is available in the tissue, but the distinct increase shown in Fig. 1 (0·8 kPa/min) also indicates anaerobic metabolism. The carbon dioxide produced in skin by aerobic metabolism following occlusion of blood flow only involves a tc-$P\mathrm{CO}_2$ increase of 0·2 kPa (at 45°C) (Severinghaus *et al.* 1978). Lactic acid production during anaerobic metabolism increases dissolved CO_2 in extracellular fluid (Rooth *et al.* 1985) and this slower process may explain the delayed onset of tc-$P\mathrm{CO}_2$ changes and the increased values following the compression. Pressure between the fetal head and the cervix during labour is often two to three times the intra-amniotic pressure (Lindgren 1977) when measured near to the equator of the fetal head. Consequently, a weight of >100 g applied on the electrode (i.e. 52 g/cm^2 or 39·8 mmHg) in the lateral position will not be uncommon. As fetal arterial systolic blood pressure, 60–70 mmHg (Young 1961), is lower than in newborn infants, compromised capillary blood flow may develop at lower compression in the fetus during labour. Figure 3 demonstrates delayed elevations of tc-$P\mathrm{CO}_2$ after uterine contractions. The fact that only the lateral electrode is affected by the uterine contractions contradicts the theory of the tonsure effect (O'Connor & Hytten 1979). According to this theory, the equatorial compression of the fetal head should compromise the blood flow of the scalp and involve decreased values of $P\mathrm{O}_2$ and pH and increased values of $P\mathrm{CO}_2$ when measured in capillary blood or trans-

Table 1. Simultaneous transcutaneous CO_2 tension (tc-$P\mathrm{CO}_2$) measurements from two electrodes placed in the central or lateral position of cervical os

		tc-$P\mathrm{CO}_2$ (kPa)			Significance	
Cervical dilatation	*NS*	Central position	Lateral position	Difference*	*t*	*P*
<8 cm	36	8·4 (1·3)	9·3 (1·5)	0·9 (1·5)	3·36	<0·005
≥8 cm	40	9·2 (1·6)	9·5 (1·4)	0·3 (1·6)	1·36	NS
Total	76	8·8 (1·5)	9·4 (1·4)	0·6 (1·6)	3·42	<0·005

Results are mean (SD) values.

* Mean of the differences between paired simultaneous measurements from the central and lateral electrodes (two-tailed paired *t*-test).

cutaneously on the scalp. The close correlation between tc-$P\text{CO}_2$ measured just before delivery and the $P\text{CO}_2$ of the umbilical artery blood just after delivery (Nickelsen *et al.* 1986) likewise states that the tonsure effect usually does not affect tc-$P\text{O}_2$ measurements.

As expected the significant difference between simultaneous readings of the lateral and central electrode disappears at a cervical dilatation of ≥8 cm, when both electrodes are free of the cervical edge. Compression of the electrode between the pelvic floor and the fetal head may influence the reading in a similar way, but the central electrode will be affected as often as the lateral.

From this study we conclude that the tonsure effect, which may invalidate tc-$P\text{O}_2$ measurements during labour (Wallenburg *et al.* 1984), does not affect tc-$P\text{CO}_2$ measurements, but compression of the electrode induces elevated tc-$P\text{CO}_2$ values. To avoid spuriously high tc-$P\text{CO}_2$ values the electrode should be placed in an area free of compression from the cervix and the pelvic floor.

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Magnetic resonance imaging—its application to cervical carcinoma

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Summary. Twenty-five women with primary carcinoma of the cervix were examined with magnetic resonance imaging (MRI). A number of different pulse sequences with T_1 and T_2 weighting were employed to determine optimum tissue contrast, and the potential for staging cervical cancer was assessed and compared with the clinical findings. MRI is seen to give a unique view of cervical cancer in particular in stage I and II disease where other imaging techniques have known limitations. In addition, stages III and IV were well seen with demonstration of tumour comparable with that of computerized axial tomography (CT).

Carcinoma of the cervix is the second most common gynaecological cancer. The prognosis is determined by the stage of disease at the time of diagnosis with a 50% 5-year survival rate in those with invasive disease. Accurate staging at presentation is therefore important in order to assess prognosis, and to choose and compare different treatments. At present, cervical cancer is staged according to clinical findings (FIGO 1972) but many studies have demonstrated an error of 34%–39% in comparing clinical with surgical stage (van Nagell *et al.* 1971; Averette *et al.* 1975). Computerized axial tomography (CT) has improved the assessment but has some limitations (Brenner *et al.* 1982). Therefore, new techniques with the potential of improving the staging and assessment of these tumours merit investigation. Magnetic resonance imaging (MRI) is a recently introduced imaging technique which employs radiofrequency radiation in the presence of a magnetic field to create cross-sectional images of the body. MRI has already gained acceptance in the central nervous and musculoskeletal systems (Worthington 1983).

The application of MRI to the female pelvis is currently on trial, and initial results have shown that it may have important implications in the staging and assessment of gynaecological cancer (Powell *et al.* 1986). The pelvis is suitable for examination because of the minimal effect on the pelvic organs from respiratory motion. MRI offers the specific advantages of multiplanar imaging, avoids the use of ionizing radiation and when used appropriately is without known hazard. In addition, by altering the pattern of radiofrequency applied to the so-called pulse sequences, images can be produced weighted differently by proton density and the relaxation times T_1 and T_2.

This study was designed as an initial assessment of magnetic resonance in carcinoma of the cervix, to determine the appropriate pulse sequences to maximize tissue contrast and to assess the ability of MRI to stage the primary

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cervical cancer in comparison with clinical staging.

Subjects and methods

MRI was performed on 25 consecutive patients with newly diagnosed, untreated cervical cancer. Histological diagnosis was established by cervical biopsy, vaginal biopsy or dilatation and curettage. Routine clinical staging included physical examination, chest X-ray, cystoscopy, intravenous ureterogram and barium enema in selected patients. Clinical staging was based on the International Federation of Gynaecology and Obstetrics (FIGO 1971) staging classification.

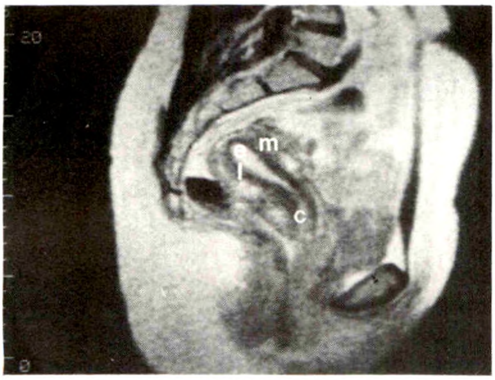


Fig. 1a. Sagittal view—normal retroverted uterus. Low intensity band (1); myometrium (m); endometrium (e); cervix (c). TE 80 ms, TR 1000 ms.

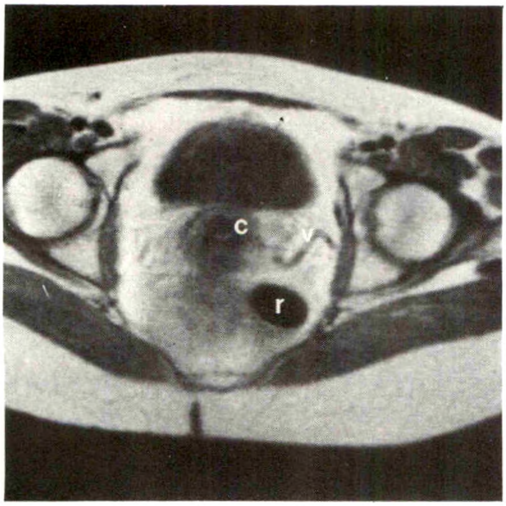


Fig. 1b. Transverse axial view through normal cervix (c), rectum (r), uterine vessel (v). TE 40 ms, TR 1000 ms.

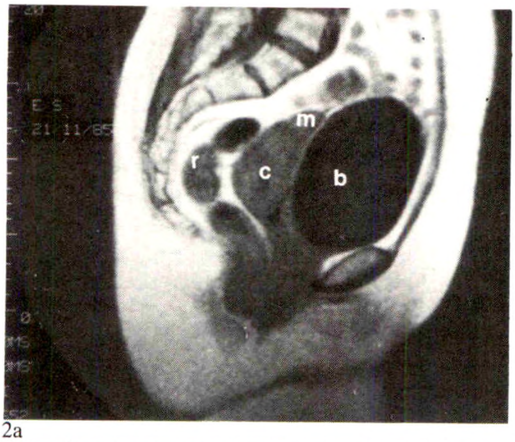
The MRI stage was assessed from objective findings without knowledge of the clinical stage or pelvic examination. The patients were between 25 and 75 years of age (mean 49 years). Clinical stages were I(7), IIa(5), IIb(6), IIIa(2), IIIb(4), IV(1). Histological diagnoses were squamous carcinoma in 20 patients and adenocarcinoma in five patients.

MRI was performed on a 0·15 Tesla imaging system based on a resistive magnet (Picker). Images were acquired and displayed on a 256 × 256 matrix yielding a pixel size of 0·8 mm × 0·8 mm. A number of different spin sequences were employed to give both T_2 weighted (spin echo) and T_1 weighted (inversion recovery) images. Coronal, transverse and sagittal planes were evaluated to determine the optimum image plane. Both single and multislice protocols were available. Imaging time for evaluation was usually less than 1 hour. MRI is carried out in the UK under the guidelines laid down by the National (British) Radiological Protection Board (NRPB 1983). Informed consent is obtained before examination in each patient.

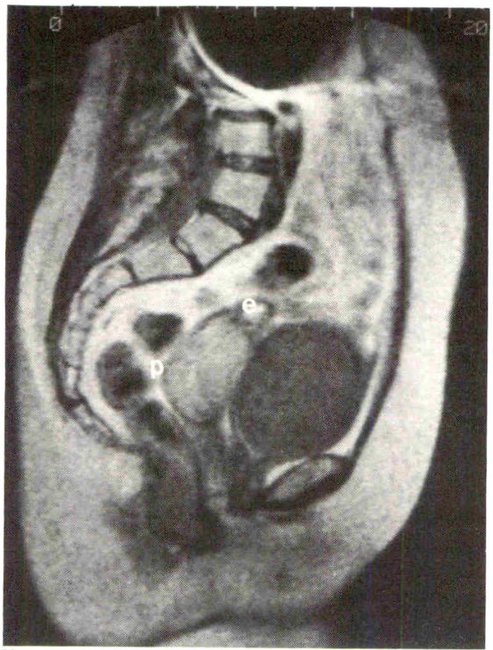
Results

An initial appraisal of the appearance of the normal cervix as seen by MRI is required before studying the changes seen in cervical cancer. Figure 1a is a T_2 weighted sagittal image of a normal retroverted uterus. A band of low signal intensity is demonstrated on the inner aspect of the myometrium and is seen to continue into the cervix to border the cervical canal. The anatomical substrate that this represents is unknown. Our preliminary studies have suggested a collagenous origin (Worthington *et al.* 1985). This appearance of the cervix is not seen with ultrasound or computerized axial tomography (CT). The cervical band assists in the location of the cervix in the transverse axial plane (Fig. 1b). The availability of examination in either sagittal, coronal, or transverse planes is advantageous in the assessment of local extension.

Figure 2a is a sagittal T_1 weighted image of a cervical carcinoma. The tumour has a uniform signal intensity similar to the myometrium. A clear plane separating the tumour and bladder anteriorly is visible. The tumour signal intensity, however, is seen to increase when T_2 weighted sequences are employed (Fig. 2b). The tumour is limited by a band of low intensity which appears to be breached posteriorly. The myo-



2a



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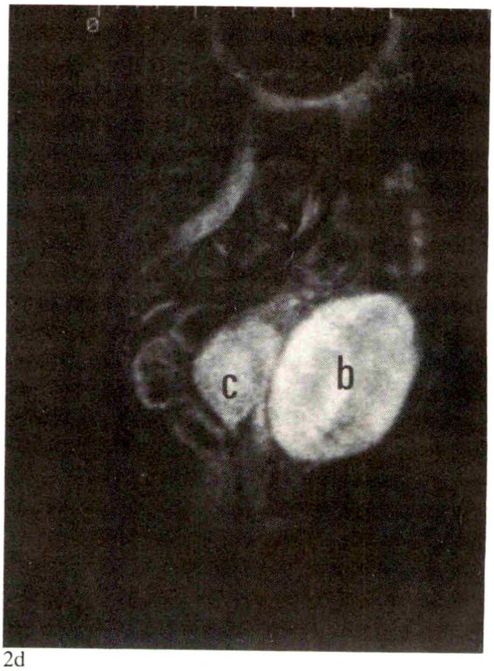
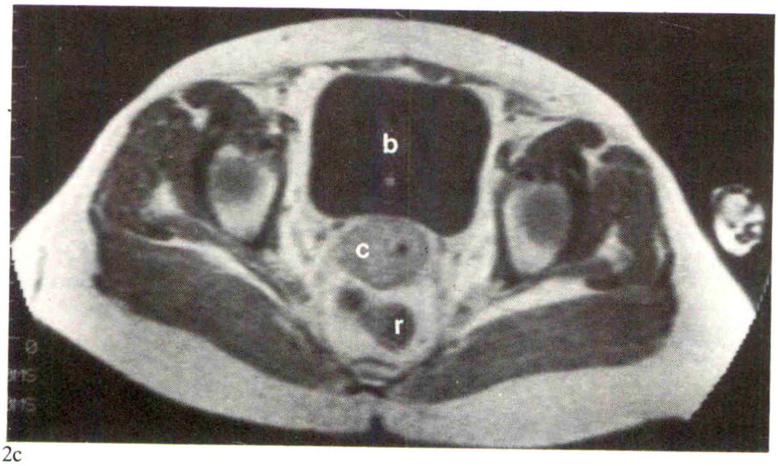


2d

Fig. 2. Sagittal view of an early cervical carcinoma (c), bladder (b), rectum (r), endometrium (e), pseudocapsule (p), myometrium (m).
Fig. 2: (a) TE 40 ms, TR 200 ms; (b) TE 80 ms, TR 1000 ms; (c) TE 40 ms, TR 1000 ms, transverse axial view; (d) TI 100 ms, TR 1500 ms.



2c

metrium and endometrium are distinct from the tumour, the upper margins of which are now clear. Although T_1 weighted sequences provide comparatively poor tissue differentiation between tumour and myometrium, the high signal intensity from pelvic fat acts as a good contrast to the tumour edge. This is best demonstrated in the transverse axial plane (Fig. 2c) and is particularly useful in regard to the assessment of parametrial spread and invasion to the pelvic side wall. The so-called STIR sequence (short TI inversion recovery sequence) (Bydder & Young 1985) when used with a suitable choice of TI the signal from pelvic fat can be suppressed and in addition T_1 and T_2 contrast becomes additive. The overall effect is to provide a greatly enhanced contrast between tumour and the surrounding tissues (Fig. 2d). Many pathological conditions such as neoplasia are associated with increased T_1 and T_2 relaxation times. Consequently, the additive effect of T_1 and T_2 contrast invests this new sequence with a greater sensitivity for the detection of tumour tissue. The tumour has a high signal intensity in sharp contrast to the surrounding tissue. As well as providing information in regard to local tumour extent, there is some evidence to suggest that the sequence will be of value in differentiating fibrosis consequent to radiotherapy from tumour recurrence.

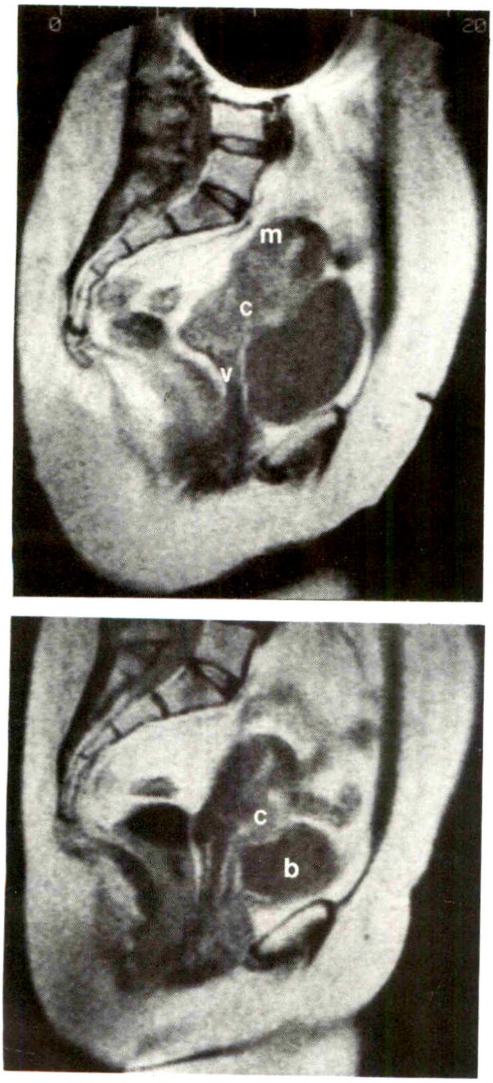


Fig. 3. (a, *top*) Sagittal view of a FIGO stage IIb cervical carcinoma (c). Tumour is invading myometrium (m) and is on to anterior vaginal wall (v). TE 80ms, TR 1000ms. (b, *bottom*) 3 months after radiotherapy increase in tumour anteriorly (c) invading into bladder (b). TE 80 ms, TR 1000 ms.

The sagittal plane of view is the most appropriate for assessment of myometrial involvement. Figure 3a is a tumour which was clinically thought to be a stage IIb. The tumour has extended onto the upper third of the anterior vaginal wall. The extent of involvement of the body of the uterus was not apparent at examination under general anaesthesia. The importance of myometrial invasion in relation to prognosis is well known (Prempree *et al.* 1982) although it is not in the present FIGO staging classification. This patient subsequently underwent a course of pelvic irradiation; the follow-up scan 3 months later shows there has been a good response posteriorly, with tumour regression. Anteriorly there is an increased amount of tumour which is now indenting the bladder and obscuring the plane between them suggesting involvement of the bladder (Fig. 3b). The sagittal plane is more valuable than the transverse axial in determining invasion of the bladder wall particularly at the bladder base. In contrast, assessment of tumour involvement of the rectum is easier with transverse axial scans. Figures 4a and 4b are MRI and CT scans of a tumour which has invaded posteriorly towards the rectum. The rectum has a layer of pelvic fat lying anteriorly which is well demonstrated with T_1 weighted pulse sequences, and assists in the assessment of tumour involvement of the rectum. The layer is also seen with CT examinations. Tumour involving the parametria is the most difficult to assess clinically, particularly in the detection of a tumour free plane medial to the obturator internus. The presence of parametrial involvement may determine whether the patient is suitable for surgery as radical hysterectomy is usually reserved for tumours confined to the cervix or with minimal vaginal extension. Radiation therapy is the treatment of choice for tumour that has spread to the parametria or beyond (Jones & Jones 1981); CT examinations have been disappointing in their assessment of parametrial extension of cervical cancer (Walsh & Goplerud 1981). In our series excellent demonstration of the parametria is seen on both coronal and transverse axial planes with MRI. Figure 5 is a T_1 weighted transverse axial image of a tumour extending into the left parametrium. Involvement of the parametria is best demonstrated with T_1 sequences which highlight the fat in contrast to the invading tumour.

More advanced lesions are equally well seen with MRI. Figure 6 is a large tumour which has a central necrotic area with extension and involvement of both pelvic side walls. The central necrosis demonstrated is commonly seen with the larger tumours and is also a feature visible with CT (Engelshoven 1983).

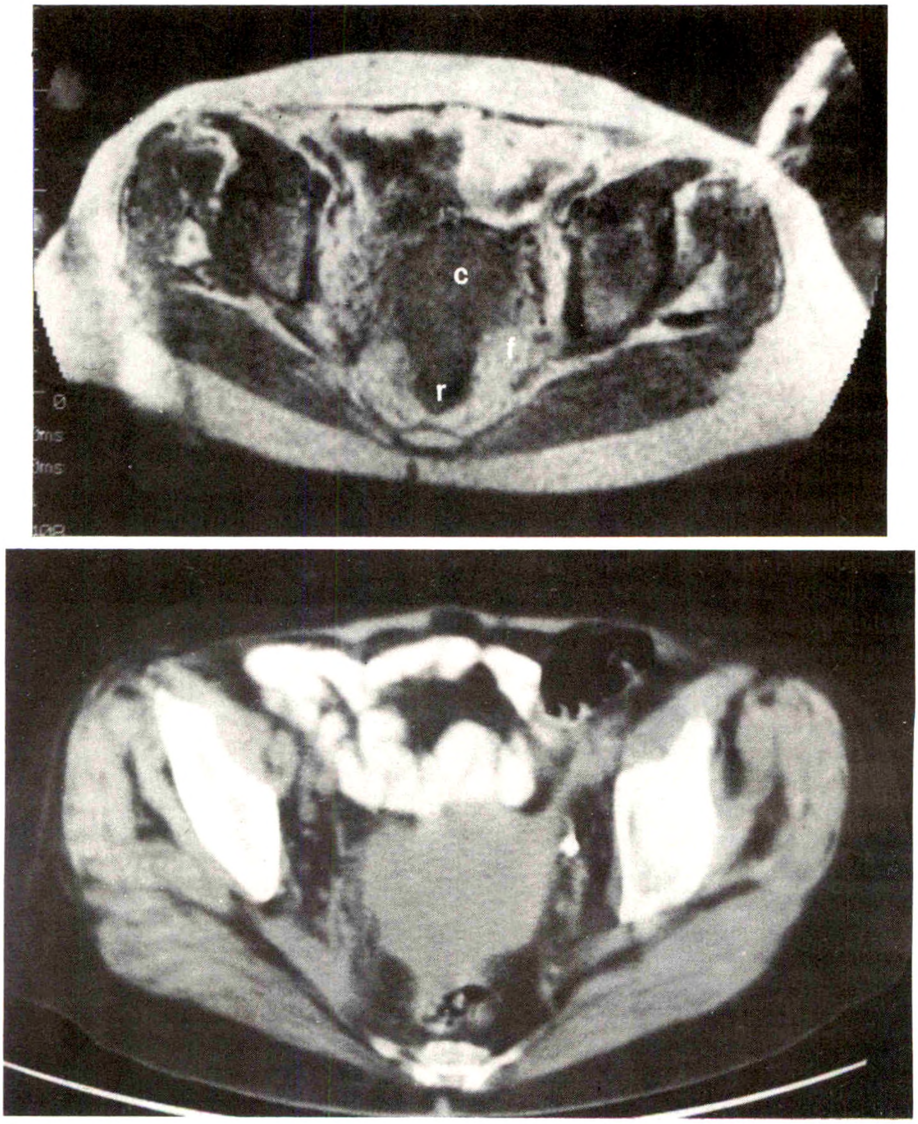


Fig. 4. (a, *top*) Transverse axial view of a cervical tumour (c) invading posteriorly to involve rectum (r) fat (f). TI 600 ms, TR 2000 ms. (b, *bottom*) Transverse axial CT scan at same level.

Lymph nodes and recurrent disease

The assessment of lymphatic involvement by MRI in carcinomas of the cervix has still to be determined. Figure 7 is a T_1 weighted transverse axial image of a patient with a central recurrence associated with a collection of lymph nodes on the pelvic side wall. The glands have a uniform signal similar to that of the tumour tissue, and tumour within the lymphatic tissue does not have a distinguishing signal. Therefore MRI at the present time in the assessment of lymph nodes relies on similar criteria as for CT, i.e. an alteration in the morphology of the glands before diagnosis of involvement can be confidently made.

Although not specifically a part of the study, in six patients examined with recurrent tumour, a similar range of signal intensities was exhibited to that of the primary growth, i.e. when the T_2 weighting of the pulse sequence increases the signal intensity of the recurrent tumour tissue increases. This is opposite to the behaviour of fibrous tissue which decreases in signal intensity when the T_2 weighting lengthens. Figure 8 is a T_2 weighted transverse axial image of a large recurrence in the pelvis to which bowel is closely applied, subsequently confirmed at laparotomy.

Stage correlation

MRI stage in 25 patients is compared with clini-

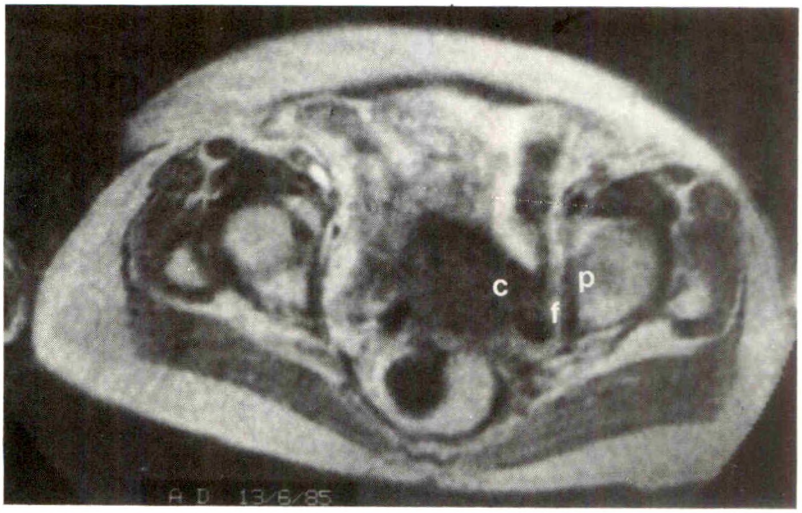


Fig. 5. Transverse axial view, fat plane (f) is seen between tumour (c) and pelvic side wall (p). TI 500 ms, TR 2000 ms.

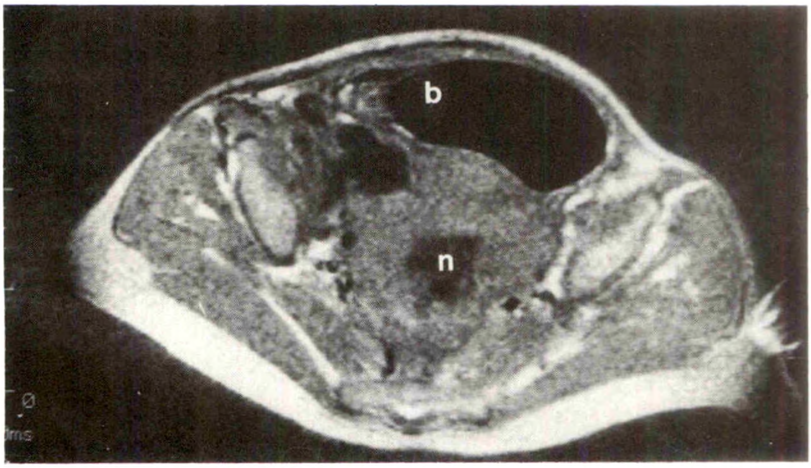


Fig. 6. Transverse axial view, FIGO stage IV cervical carcinoma. Extends to pelvic side walls and bladder (b). Large central necrotic area (n). TI 600 ms, TR 2000 ms.

cal stage in Table 1. MRI and clinical stage were identical in 12 (48%) patients. MRI indicated more advance disease than clinical examination in 10 (40%) patients and less extensive disease in 3 (12%). Eleven patients subsequently underwent surgery, and the surgical stage and MRI stage for nine are given in Table 2; two patients underwent prior radiotherapy and at histopathological examination no tumour tissue was demonstrable. In eight of the nine patients the surgical stage agreed with the MRI findings. In one patient MRI had indicated that there was involvement of the parametrium which was also suggested by the CT examination but subsequently was not confirmed at surgery. The explanation for this discrepancy is uncertain.

Discussion

The clinical assessment of invasive cervical cancer is poor, particularly of parametrial spread. This is important if surgical intervention is to be contemplated. In addition, inaccuracies in clinical assessment may downstage tumours and lead to a misleading impression of tumour response to therapy. Standard radiological techniques yield little information with regard to stage. In a retrospective study of 227 patients with invasive carcinoma of the cervix, Griffin *et al.* (1976) reported tumour related findings in only 1% of chest films, 3·4% of barium enema studies and 7·3% of intravenous urograms. The value of CT in primary cervical cancer is still

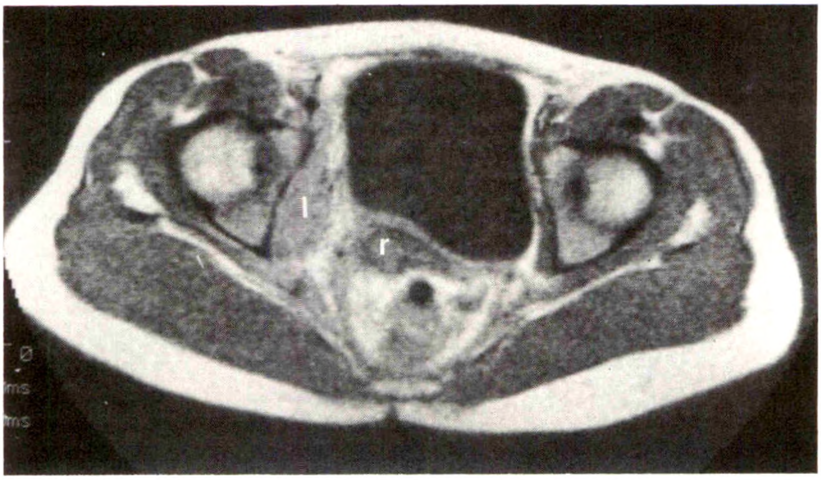


Fig. 7. Transverse axial view of a central recurrence (r) and associated group of lymph nodes (l) on the pelvic side wall. TE 40 ms, TR 500 ms.

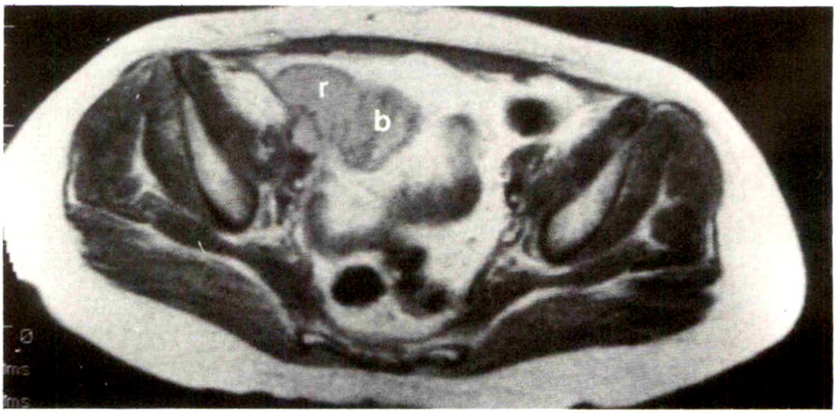


Fig. 8. Transverse axial view of a right-sided recurrent carcinoma (r) involving small bowel (b). TE 40 ms, TR 1000 ms.

questionable, problems arise involving parametrial assessment, differentiation of fibrosis from tumour in recurrent disease, and evaluation of lymph nodes (Balfe *et al.* 1985).

Magnetic resonance imaging (MRI) may offer distinct advantages over conventional radiological techniques in staging cervical tumours. In our series the primary tumour was positively identified in all cases. The sagittal plane demonstrated extension of tumour into the myometrium and extension on to the vaginal wall. In addition, parametrial extension is well depicted on both transverse axial and coronal planes. T_1 weighted images provided excellent tissue contrast between the high signal from pelvic fat and the intermediate intensity of tumour tissue enabling demonstration of involvement of the pelvic side wall. The multiplanar facilities that MRI provides for tumour assessment are not available with CT. Extension of tumour into the myometrium and vagina are poorly demonstrated by CT. The choice of pulse sequence is critical if the tumour is to be demonstrated and a combination of sequences in different planes is required.

MRI stage differed from clinical stage in 13 (52%), a similar proportion to the discrepancy found between clinical and surgical staging. In comparison with clinical stage, MRI upstaged tumours in 10 (40%) and downstaged them in 3 (12%). The majority of advanced tumours were treated by radiotherapy, therefore precluding surgical correlation, but correlation in nine patients yielded some preliminary conclusions. MRI would appear to be able to differentiate in nearly all patients stage Ib from stage IIb disease. Current developments with high resolution machines should improve further the recognition of normal and abnormal parametria. In the later stages of the disease more surgically proven cases would be necessary to verify our findings, but it would appear that MRI is also suitable for imaging stage III and IV tumours.

Recent studies have demonstrated that the notion of tumour volume may be of greater value than stage for the overall prognosis of patients with cervical cancer (Baltzer 1979). A close relation exists between tumour volume and risk of lymph node metastases as well as between

Table 1. Prospective comparison between clinical and magnetic resonance imaging (MRI) stage in 25 patients with primary cervical carcinoma

		MRI stage					
Clinical stage	No. of patients	I	IIa	IIb	IIIa	IIIb	IV
I	7	**3**	1	2	1	0	0
IIa	5	0	**2**	3	0	0	0
IIb	6	0	0	**4**	0	0	2
IIIa	2	0	0	0	**1**	0	1
IIIb	4	0	0	3	0	**1**	0
IV	1	0	0	0	0	0	**1**
Total	25	3	3	12	2	1	4

Table 2. Prospective comparison between magnetic resonance imaging (MRI) stage and surgical stage in nine patients with cervical carcinoma

		Surgical stage				
MRI stage	No. of patients	I	IIa	IIb	IIIa	IV
I	2	**2**	0	0	0	0
IIa	1	0	**1**	0	0	0
IIb	4	1	0	**3**	0	0
IIIa	1	0	0	0	**1**	0
IV	1	0	0	0	0	**1**
Total	9	3	1	3	1	1

the tumour volume and chances of recovery (Dargent *et al.* 1985). Because of the three-dimensional display provided by MRI, a quantitative assessment of tumour volume may be obtained. The assessment of patients with suspected recurrent cancer may be difficult due to prior radiotherapy or surgery, and errors estimating disease extent are frequent. The prognosis in this group is poor, with a 1-year survival of 15% (Van Nagell *et al.* 1979). Earlier detection may be a way of improving this dismal statistic. CT was found in a recent series to have an accuracy of 82% in predicting recurrent disease (Walsh *et al.* 1981), but has a major drawback in its ability to distinguish reliably between radiation fibrosis and recurrent tumour. Radiation fibrosis has a low signal intensity similar to muscle on both T_1 and T_2 weighted pulse sequences. In contrast recurrent tumour has a higher signal intensity when longer T_2 weighted pulse sequences are employed (Glazer *et al.* 1985). Recurrent cervical carcinoma in our study has shown similar characteristics, and it is anticipated that the diagnostic potential of MRI will be further improved with the introduction of paramagnetic contrast agents.

Examination of lymphatic tissues is more problematic. Diagnosis of lymph node involvement by CT relies on the gland being greater than 1·5–2 cm diameter (Lee *et al.* 1978). A preliminary study of lymph glands with MRI has demonstrated that measurements of the relaxation times of the gland (the T_1 and T_2 times) may indicate metastic involvement with tumour although not apparent on the image itself (Dooms *et al.* 1985).

Gadolinium DTPA is a paramagnetic contrast agent which after intravenous injection has a distribution similar to that of iodinated media used in CT. Accumulation in the tissues results in a reduction in the relaxation time. This has been found to be of value in the central nervous system (Carr *et al.* 1984) and there is hope that the diagnostic potential of MRI in the assessment of lymphadenopathy and recurrent disease in the pelvis will be improved. A trial is currently in progress in Nottingham using Gadolinium DTPA in patients with cervical cancer, which it is anticipated will increase the detection of metastatic disease in lymph nodes and recurrent tumour.

Magnetic resonance images have also successfully transferred to radiotherapy localization films (Daffner *et al.* 1985), the distinct advantage being the ability to produce direct sagittal or coronal images of the area of interest. This is particularly useful when planning radiation fields for the treatment of soft tissue neoplasms, since the treatment portals are usually based on conventional frontal and lateral radiographs and the palpable abnormality. The more accurate localization of tumour before radiotherapy may produce a better therapeutic ratio by spanning normal tissue and allowing a higher dose of radiation to the neoplasm.

Therefore, MRI would appear to have distinct advantages in relation to cervical cancer. The multiplanar, and tissue characterization properties would appear to accrue benefits, particularly in the improved staging in early disease. The demonstration of tumour extent in all stages equals or surpasses that given by other imaging techniques. This additional information will lead to a more accurate assessment of stage and therefore more propitious choice of therapy. Comparison of different treatment protocols and the visualization of tumour response is available. It is anticipated that increased resolution with a 512 × 512 matrix and newer techniques involving reductions in scanning time and the introduction of contrast agents will further improve the unique potential provided by MRI in cervical cancer.

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Ultrasonography for early detection of ovarian carcinoma

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Summary. Ultrasound scan for detection of ovarian enlargements was performed in a target group of out-patients attending the clinic for various reasons in the 40–70 years range. Overall 805 women were examined, in 99% of whom the ovaries and/or their vessels could be identified. Pathological findings were suspected in 83 patients at the first scan, and were confirmed in 50 after a repeat scan, 39 of whom subsequently underwent surgery. Various ovarian lesions were found in 35 women, including five mucinous and serous cystadenomas, one carcinoma, two borderline tumours, and a cancer of the caecum. None of the borderline or malignant ovarian lesions were found by manual pelvic examination. Ultrasound screening appears to be a useful diagnostic aid, though its usefulness might be further improved if other risk factors such as heredity and period of ovulatory activity are taken into consideration.

The prognosis for women with ovarian carcinoma is poor because of late diagnosis. Early symptoms are lacking, and by the time symptoms do appear, in 60–70% of cases, the disease has already spread. The 5-year survival rate is about 20% in advanced disease (stages III and IV) compared with almost 80% in patients with stage I disease (Sigurdsson *et al.* 1983). To improve results, a method for early detection of the disease is imperative. Various tumour markers have not hitherto proved helpful in clinical use; some monoclonal antibodies are still on trial, but their usefulness in the early detection of ovarian cancer has yet to be proved.

As a complement of manual pelvic examination, ultrasound examination might be useful in detecting enlargements of the ovaries and neoplastic growth at an early stage. Although Sundén (1964) reported that pathological changes in the ovaries could be seen with ultrasound, it was not until almost a decade later that the next report of ultrasound examination of the ovaries was published (Kratochwil *et al.* 1972). Hackelöer & Nitschke-Dabelstein (1980) showed that the ovaries could be identified by tracing the passage of the ovarian vessels. With the advent of real-time sector scanners, quick and easy identification of the ovaries became possible. The practical use of these advances is exemplified by ultrasound examination of the ovaries for puncture of the ovarian follicle in the collection of ova for in-vitro fertilization. Campbell *et al.* (1982) presented the first encouraging results from a screening programme for ovarian cancer.

We have assessed the use of ultrasound scanning in detecting ovarian enlargements in a target group of out-patients attending the clinic for various symptoms, and who belonged to the age group at risk for ovarian cancer (National Board of Health and Welfare 1981).

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Patients and methods

Ultrasound examination was offered to every woman between the ages of 40 and 70 years who contacted the out-patient clinic of the Department of Obstetrics and Gynaecology at the University of Lund during the period of the study, either for a regular check-up or for any other reason. All patients had a manual pelvic examination before the ultrasound scan. Pelvic examination was performed by one of the 30 or so experienced gynaecologists available at the clinic. Because of the study's popularity with patients and the limited availability of ultrasound, the time lapse between the pelvic examination and ultrasound scan varied between 1 and 12 weeks. The findings of the manual examination were not available to the ultrasonographer.

The ultrasound examination was performed with the full-bladder technique (Donald 1966), using a 'real-time' sector scanner (Diasonics DS 20) and a 3·5 MHz probe throughout. All examinations were made by one technician, a specially trained midwife. The uterus and the ovaries were measured in three planes, and the volume of the ovaries was calculated using a simplified version of the ellipsoid formula: length × width × depth × 0·52 (Ivarsson *et al.* 1983). Where the ovaries could not be directly identified, the examination was considered normal if the ovarian vessels could be identified or if nothing pathological could be seen in their vicinity. All patients with abnormal ovarian scans were asked to return for another scan 3–4 weeks later unless immediate surgery was considered necessary. The findings at the ultrasound examination were compared with those at pelvic examination, surgery and with subsequent histological examination.

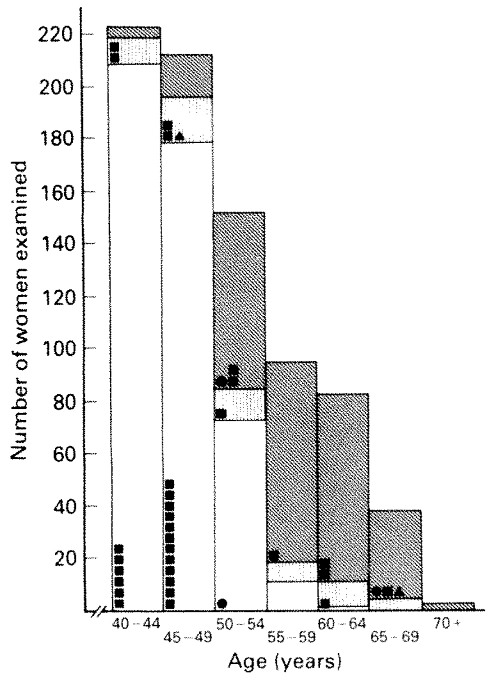

Fig. 1. Distribution by age and menstrual status of 805 women examined by ultrasound. The distribution of pathological findings in the 35 women who subsequently underwent laparotomy is indicated. ▨ Postmenopausal; ▥ hysterectomized; ☐ premenopausal. (●) Malignant/borderline ovarian tumour; (■) benign ovarian tumour/gynaecological lesion; (▲) non-gynaecological lesion.

Results

A total of 805 patients were examined during the second half of 1983 and the first months of 1984. Their distribution in relation to age and menstrual status is shown in Fig. 1. Both ovaries and/or their vessels could be identified in 795 of the patients (99%). The reasons for failure were obesity, uterine fibroids or an inadequately filled bladder.

As shown in Table 1, ovarian findings in 712 women were normal on the first ultrasound scan; in two of these, suspected ovarian enlargements were found on manual examination, sigmoiditis being diagnosed in one while the second was normal at the check-up manual examination. Of the 83 patients with ovarian pathology detected at the first scan, 72 were considered normal and 11 abnormal on manual examination, but when these 83 women were subjected to a repeat scan, the number with pathological findings was reduced to 50, 39 of whom subsequently had a laparotomy. Of the remaining 11 women, one was known to have endometriosis, one was lost to follow-up when she moved from the area, and nine were followed up elsewhere, outside the study.

The macroscopic and histological findings of the 39 patients who underwent surgery are given in Table 2. Lesions were present in 35 but absent in four, three of whom did not have a repeat scan the day before surgery, 5 or 6 weeks having elapsed since their pathological ultrasound examination. Laparoscopy was performed in

Table 1. Findings on manual pelvic examination compared to those on ultrasound scan in 795 women with ovaries identified at ultrasound examination

	Ultrasound examination	
	Normal (712)	Pathological (83)
Normal manual pelvic examination (782)	710	72
Pathological (13)	2	11

two patients showing normal ovarian findings; the third patient had a hysterectomy for other reasons 2 months after the pathological scan, the delay being due to intercurrent disease. In the fourth patient, though the scan was normal the day before operation, a laparoscopy was performed because of pelvic pain. Of the 35 lesions, 31 were benign including five mucinous and serous cystadenomas, three were malignant or borderline ovarian tumours, one was sigmoiditis but at the same time a carcinoma of the caecum was accidentally found. The diagnoses of the 35 patients with lesions found at surgery are also shown in Fig. 1, where they are related to age and menstrual status.

The three patients with malignant or borderline ovarian lesions had pathological ultrasound scans, but normal manual pelvic examinations. Of the two borderline ovarian tumours, one was 6 cm in diameter (mucinous cystadenoma) and the other 4 cm (proliferating cystadenofibroma). The ovarian carcinoma was of endometrial type, stage III.

Table 2. Findings in the 39 patients subjected to surgery because of an abnormal ultrasound scan

Diagnosis	Normal manual pelvic examination	Abnormal manual pelvic examination
Simple cystadenoma	12	6
Serous cystadenoma	1	
Seropapillary cystadenoma	1	1
Mucinous cystadenoma	1	1
Borderline tumour	2	
Ovarian carcinoma	1	
Dermoid cyst	1	
Endometriosis	3	
Paraovarian cyst	1	
Hydrosalpinx	1	
Myoma	1	
Cancer of the caecum	1	
Retroperitoneal lymphangioma	1	
Normal findings	4	
Total	31	8

Discussion

In the present study the ovaries and/or their vessels were identified in 99% of patients, similar to the proportion of 99·4% reported by Goswamy *et al.* (1983). With the advent of sector scanners and the real-time technique, the possibility of viewing the ovaries has been much improved. Cysts can be distinguished from intestinal loops by the absence of peristalsis, and the identification of ovarian vessels has proved helpful.

Our survey detected abnormal ovarian findings in 83 (10·3%) of the total of 805 patients. This includes one carcinoma, two borderline tumours, five mucinous and serous cystadenomas, and a cancer of the caecum. In a total of 1084 patients, Goswamy *et al.* (1983) found pathological ovarian enlargements in 3%, including one clear-cell carcinoma and five mucinous and serous cystadenomas. This difference might be explained by the fact that all our patients had contacted the clinic on their own initiative for one reason or another, whereas Goswamy *et al.* (1983) obtained their subjects in response to a general invitation published in the popular press. Thus the proportion of women at risk in our study should be greater.

We also had a higher percentage of benign cysts at the first scan, which might be due to the comparative youth of our patients, only about a third of whom were of postmenopausal age. A repeat scan reduced the number of ovarian enlargements by 40% from 83 to 50. Presumably a number of simple follicular or luteal cysts disappeared during the interval between the two examinations.

An objection to ovarian ultrasound scanning for early detection of ovarian carcinoma is that it tends to lead to unnecessary surgery for non-malignant lesions, but such cases were found to be few. Correct diagnosis, even of benign lesions such as endometriosis, is certainly of value and the removal of serous and mucinous cystadenomas might in some cases prevent malignant degeneration.

Of the 39 enlargements found at ultrasonography, only eight were found on manual examination, and none of the three borderline or malignant lesions was found by clinical examination. This indicates that ultrasound examination of the ovaries is superior to palpation, but in the one case of ovarian carcinoma, uterine fibroids were suspected at the pelvic examination, whereas both an ovarian tumour, enlarged ovaries, and uterine fibroids were suspected at ultrasound. As it turned out, an adenocarcinoma of endometrial type stage III was found, but uterine fibroids were absent, which shows that metastasis of ovarian tumours and fibroids are hard to differentiate even with ultrasound.

The results of the study indicate that in a selected group of women at risk, the use of ultrasound screening would be justified for early detection of ovarian cancer. Its use might be even more advantageous if other risk factors such as heredity and period of ovulatory activity were also to be taken into consideration.

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The effects of norethisterone in postmenopausal women on oestrogen replacement therapy: a model for the premenstrual syndrome

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Summary. The influence of norethisterone on mood and behaviour was investigated in prospective placebo-controlled study in 58 postmenopausal hysterectomized women who were being treated with subcutaneous oestradiol and testosterone implants. Norethisterone, 2·5 or 5 mg daily, was given for 7 days and a placebo for two periods of 7 days. Psychological, behavioural and physical variables were assessed using the Menstrual Distress Questionnaire. There were widespread adverse effects which were dose-related. Significant changes in five of the eight symptom complexes studied (pain, concentration, behavioural change, water retention and negative affect) were found with 5 mg/day of the progestogen. The symptoms were similar to the typical complaints of the premenstrual syndrome, such that a combination of oestradiol and testosterone implants with cyclical oral norethisterone appears to be a model for this condition. The dose of this progestogen should therefore be the minimum to achieve the desired therapeutic effect.

Much attention has been focused on the mood and behavioural changes associated with the combined contraceptive pill, in particular depression. Most women do not experience any significant psychological effects (Glick & Bennett 1982). Some gain positive benefits from therapy (Worsley 1980), not least because of the relief from the fear of pregnancy, while depression and other symptoms have been reported in 0–50% of oral contraceptive users (Kane 1976). The response is thus highly variable, and depends to some extent on the duration of therapy, pretreatment morbidity, weight, social factors, and the steroids concerned. Problems with the combined pill appear to be more prevalent at the start of therapy (Cullberg *et al.* 1969), and in women with psychiatric or emotional disturbances, as well as obesity (Nilsson *et al.* 1967). Conversely, beneficial reactions in certain psychotic illnesses, including depression, have also been reported (Felthous *et al.* 1980).

If there is a pharmacological effect on mood and behaviour, the separate effects of the oestrogenic and progestogenic components are unclear. Most information comes from studies looking at the response to variable doses of the two steroids in combination, but the results are conflicting. Thus, both hormones have been suggested to be individually responsible for not only

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positive but also negative psychological and behavioural phenomena (Worsley 1980; Klaiber *et al.* 1982), although an effect of the two acting together cannot be excluded. Certainly, the progestogen recommended for menopausal women receiving long-term oestrogen replacement therapy is often associated with side-effects which limit the acceptability of combined treatment.

Postmenopausal women who have had a hysterectomy and receive hormone replacement therapy in the form of subcutaneous implants of oestradiol (Studd & Thom 1981*a*) are an ideal population to study the specific symptomatic effects of progestogens under controlled conditions. Firstly, they are not subject to the cyclical variations of the pituitary-hypothalamic-ovarian axis, with their associated physiological, psychological and behavioural changes (Magos & Studd 1985). Secondly, unlike younger women receiving synthetic oestrogens or menopausal women treated with oral natural oestrogens, plasma oestradiol and oestrone concentrations following a standard 50 mg implant remain in the normal follicular range (Thom *et al.* 1981), even after long-term therapy (Cardozo *et al.* 1984). Thirdly, the effects of additional progestogen can be studied easily without withdrawal bleeding complicating the assessment. We therefore studied the physical and psychological effects of the 19-norsteroid progestogen, norethisterone, under double-blind, placebo-controlled conditions using such a model. Any cyclical mood changes found in this study would be relevant to the treatment of the climacteric as well as to a better understanding of the effects of the combined contraceptive pill.

Patients and method

The study included 70 women, with an average age of 48·3 years (range 35–63 years) who were recruited from the Menopause Clinic at Dulwich Hospital. All had had hysterectomies for non-malignant conditions within the previous 22 years (mean 11·2, SD 3·4), and were proven to be postmenopausal either by a history of bilateral salpingo-oophorectomy, or by a plasma FSH measurement of >20 i.u./l before hormone replacement therapy (Chakravarti *et al.* 1979). All were receiving treatment for climacteric complaints with subcutaneous oestradiol (50 mg) and testosterone (100 mg) implants (Organon) at regular intervals (Studd *et al.* 1977), and were asymptomatic at the time of the study; the average duration of implant hormone replacement therapy for the group was 2·1 years (range 0·5–7·5 years). None was complaining of medical, psychiatric or social problems or were taking other medication.

Therapy

Two doses of oral norethisterone (Syntex Pharmaceuticals), 5 mg (first 50 patients) and 2·5 mg (next 20 patients), were assessed under double-blind, placebo-controlled conditions using a five-period design, each period representing 1 week. The first and last periods were used as baseline, and were tablet-free. Norethisterone and an identical placebo were allocated during the middle three periods according to the case record number as follows:

Even number: Baseline/Norethisterone/Placebo/Placebo/Baseline.

Odd number: Baseline/Placebo/Norethisterone/Placebo/Baseline.

This design was chosen to (i) provide a washout period between the active and inert preparations, (ii) minimize patient expectations of the next set of tablets and (iii) give two 7-day periods of assessment for each patient and thus paired data. For these reasons, data from the placebo period immediately after a norethisterone period were ignored, leaving two baseline, one active and one inert period for analysis for each member of the study group. Even number: Baseline/Norethisterone/(PLACEBO)/Placebo/Baseline. Odd number: Baseline/Placebo/Norethisterone/(PLACEBO)/Baseline.

Assessment of symptoms

Physical, psychological and behavioural variables were assessed using a modified Moos Menstrual Distress Questionnaire (MDQ) (Moos 1969). The questionnaire consisted of a total of 45 items grouped into eight complexes (Table 1), six containing negative symptoms and behavioural patterns (pain, concentration, behavioural change, autonomic reactions, water retention and negative affect), one positive (arousal), and one non-specific adverse symptoms designed to detect 'complainers' (control). The MDQ was completed daily during the study, each item being scored on a scale of 0 (no/none)

Table 1. Modified Moos Menstrual Distress Questionnaire

(A) *Pain*
- Muscle stiffness
- Headaches
- Stomach pains
- Backache
- Tiredness
- General aches and pains

(B) *Concentration*
- Difficulty sleeping
- Forgetfulness
- Confusion
- Difficulty concentrating
- Clumsiness
- Accidents (e.g. cutting finger)
- Difficulty making decisions

(C) *Behavioural change*
- Lowered work performance
- Take naps, stay in bed
- Staying at home from work
- Avoid social activities
- Loss of efficiency

(D) *Autonomic reactions*
- Dizziness, faintness
- Cold sweats
- Feeling sick, vomiting
- Hot flushes

(E) *Water retention*
- Gain in weight
- Skin disorders (e.g. rash)
- Painful or swollen breasts
- Feeling swollen or bloated

(F) *Negative affect*
- Crying spells
- Loneliness
- Anxiety
- Restlessness
- Irritability
- Mood swings
- Depression
- Tension

(G) *Arousal*
- Feeling affectionate
- Orderliness
- Excitement
- Feelings of well-being
- Bursts of energy or activity

(H) *Control*
- Feelings of suffocation
- Chest pains
- Ringing in the ears
- Numbness, tingling
- Blind spots, fuzzy vision

to 3 (severe/a lot). For each symptom complex the total scores during the placebo (P), norethisterone (N) and the average of the two baseline (B) periods were standardized as the average daily score per symptom in the complex.

Statistics

For both doses, an overall comparison of the three treatment periods (B, P and N) were made using non-parametric analysis of variance (Friedman's test). The specific effects of the active and inert preparations were compared using Scheffé's pair-wise test for multiple comparisons.

Results

Of the 70 women recruited, 12 provided inadequate data and were excluded from the analysis. The remaining 58 included 39 treated with 5 mg and 19 with 2·5 mg doses of norethisterone and placebo. An order effect of the medication was not observed as the mean group scores for the three periods of the two allocation groups were comparable.

Norethisterone 5 mg

This dose of progestogen was associated with increased scores for all the adverse symptom complexes (Fig. 1), and this action remained statistically significant compared with placebo for all except 'autonomic reactions' (Table 2). The greatest effects were on the psychological symptoms such as depression, anxiety and irritability (negative affect). There were no significant changes in either the positive (arousal) or the non-specific (control) symptom complexes.

Norethisterone 2·5 mg

Although there was a trend for greater reporting of adverse effects (Fig. 2), the lower dose of the progestogen did not cause any statistically significant changes in symptomatology or behaviour when compared with placebo (Table 3).

Placebo

Almost all symptoms worsened with placebo, including significant changes in the items under 'concentration', 'autonomic reactions' and 'water retention' (Tables 2 and 3). However, this response to placebo was considerably less than to either doses of the active agent (Figs 1 and 2).

Discussion

There are several theoretical reasons why the female sex hormones should affect mood and behaviour. Both steroids accumulate and are metabolized in the brain, including the cortex (Backstrom 1977); the activity of the central nervous system appears to be increased by oestrogen, and decreased by progesterone (Vogel *et al.* 1971). Specific actions have been shown on neurotransmitters and their precursors (Asso 1983), and peptides such as

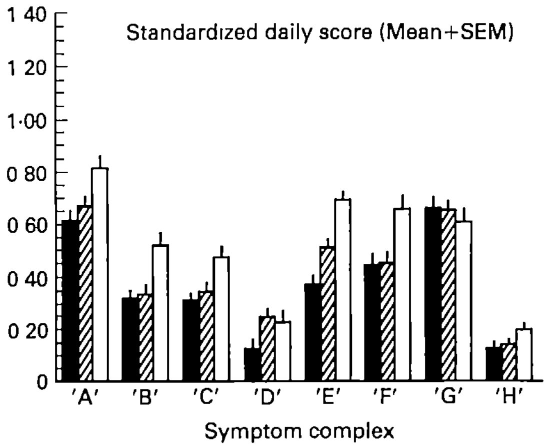

Fig. 1. Effects on the eight symptom complexes of placebo and norethisterone 5 mg daily. Symptoms scored on a scale of 0 (no/none) to 3 (severe/a lot): 'A' Pain; 'B' Concentration; 'C' Behavioural change; 'D' Autonomic reactions; 'E' Water retention; 'F' Negative affect; 'G' Arousal; 'H' Control. (■) Baseline; (▨) placebo; (□) norethisterone.

gonadotrophin-releasing factor (Nemeroff 1978) and endorphins (Reid & Yen 1981) have all been implicated in psychological functioning. For example, a deficiency of catecholamines may be involved in the pathogenesis of depression (Schidlkraut 1965) and oestrogens may act as anti-depressant by enhancing central adrenergic activity with an effect on synthesis, degradation, and neuronal uptake (Klaiber *et al.* 1982). Conversely, progesterone has some opposite properties and hence could cause depression (Beattie *et al.* 1973; Klaiber *et al.* 1971). However, the relation between hormones and the psyche is complex and ill-understood; for instance, depressed women have been found to have elevated plasma oestradiol levels compared with non-depressed controls (Vogel *et al.* 1979).

Our results show widespread, dose-related adverse effects on psychological, behavioural and physical variables by the synthetic 19-nor-steroid, norethisterone, under conditions of physiological oestrogen constancy. These data are not strictly comparable to previous studies of combined oestrogen/progestogen preparations or of progestogens (and progesterone) alone, which, if one is interested purely in the actions of progestational agents, can be criticised on a variety of grounds. Apart from the uncontrolled nature of many of these reports, response could

Table 2. Statistical analysis of the effects of norethisterone 5 mg daily

	Statistics			
Symptom complex	B *vs* N *vs* P	B *vs* N	B *vs* P	N *vs* P
Pain	<0·04	<0·02	NS	<0·025
Concentration	<0·001	<0·0001	<0·05	<0·05
Behavioural change	<0·02	<0·02	NS	<0·05
Autonomic reactions	<0·01	<0·005	<0·001	NS
Water retention	<0·0001	<0·0001	<0·02	<0·04
Negative affect	<0·01	<0·001	NS	<0·002
Arousal	NS	NS	NS	NS
Control	<0·01	NS	NS	NS

B, Baseline; N, norethisterone; P, placebo.
NS, Not significant ($P > 0·05$).

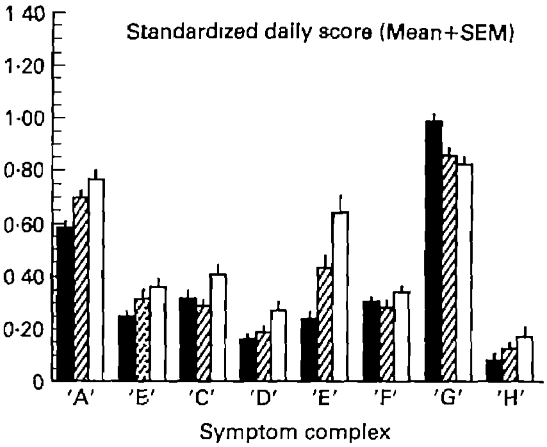

Fig. 2. Effects on the eight symptom complexes of placebo and norethisterone 2.5 mg daily. See Fig 1.

also have been influenced by one or more of the following factors: (a) sub-physiological plasma concentrations of the ovarian oestrogens when potent synthetic oestrogens were also used (Lorraine *et al.* 1965), (b) the effects of the synthetic oestrogens themselves, (c) fluctuating hormone values in women with ovarian activity, (d) sex-related differences when men formed the study group (Little *et al.* 1974), and (e) patients with psychiatric ill-health, often studied, may have responded differently to healthy subjects (Kane *et al.* 1967). With these limitations, such studies have generally suggested a sedative, anxiolytic action (Herrmann & Beach 1978), and, with progesterone, even hypnosis after large doses (Merryman 1967). Our study design was not compromised by any of the above factors, and appears to show a detrimental effect on many aspects of mood and behaviour, although a specific tranquillizing action cannot be excluded.

The symptoms secondary to norethisterone under conditions of steady-state follicular range plasma oestrogen concentration are remarkably similar to the typical complaints of the premenstrual syndrome (Magos & Studd 1984*a*). The aetiology of this common problem remains obscure, but ovarian activity most probably plays a primary role (Studd 1979; Magos & Studd 1984*b*). Our results suggest that oestradiol implants in combination with cyclical norethisterone represent a model for the syndrome, and this must give some insight into the pathophysiological mechanisms for some of the symptoms, and a clue to successful therapy. This model explains why the combined contraceptive pill is often ineffective in the treatment of the premenstrual syndrome (Goldzeiher *et al.* 1971), where the benefits of anovulation may be

Table 3. Statistical analysis of the effects of norethisterone 2·5 mg daily

	Statistics			
Symptom complex	B *vs* N *vs* P	B *vs* N	B *vs* P	N *vs* P
Pain	<0·03	<0·01	NS	NS
Concentration	NS	NS	NS	NS
Behavioural change	NS	NS	NS	NS
Autonomic reactions	NS	<0·03	NS	NS
Water retention	<0·032	<0·0001	<0·025	NS
Negative affect	NS	NS	NS	NS
Arousal	NS	<0·03	NS	NS
Control	NS	<0·5	NS	NS

B, Baseline; N, norethisterone; P, placebo.
NS, Not significant ($P > 0·05$).

overshadowed by the adverse mental and physical actions of the progestogen component. It also explains why progestogens, such as norethisterone, medroxyprogesterone acetate and dydrogesterone, have been shown to be ineffective for all but isolated symptoms (Ylostalo *et al.* 1982; Jordheim 1972; Haspels 1981). Whether progesterone itself is responsible for some of the mood and behavioural problems of the premenstrual syndrome remains unclear, but the finding that high dose progesterone pessaries are associated with more adverse symptoms than placebo is suggestive (Sampson 1979).

The finding of dose-related symptomatic side-effects with norethisterone has implications for the long-term oestrogen treatment in postmenopausal women. It has been clearly shown that the endometrial protection afforded by progestogens is duration dependent, in that 13 days per month seems to be optimal (Sturdee *et al.* 1978; Paterson *et al.* 1980; Studd & Thom 1981*b*). Furthermore, biochemical and morphological studies have indicated that 1 mg of norethisterone is sufficient to suppress endometrial proliferation (Siddle *et al.* 1981). There seems little doubt therefore that the currently used doses of progestogens could be safely reduced with benefit to the patient.

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Severe, accelerated postpartum hypertension associated with hyperthyroxinaemia. Case report

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Case report

A 26-year-old primiparous woman had had a history of moderate essential hypertension since the age of 23 years. At the time of diagnosis of the hypertension, 24-h collections of urine for creatinine clearance, catecholamines, metanephrines, and vanillylmandelic acid and rapid-sequence intravenous pyelography were normal. The patient's blood pressure was well controlled before pregnancy with hydrochlorothiazide and metoprolol. During the second trimester of the pregnancy, the hydrochlorothiazide and metoprolol were discontinued and the patient was placed on α-methyldopa (750 mg daily in three divided doses) with adequate blood pressure control. The α-methyldopa was increased to 1500 mg daily at 27 weeks because of moderate increase in blood pressures both at home and in the antenatal clinic. At 30 weeks, the home blood pressure rose to 180–200/110–120 mmHg and the patient was admitted to the hospital for further assessment.

Initial physical examination revealed a heart rate of 78 beats/min and a supine blood pressure of 180/115 mmHg. Abdominal and pelvic examination suggested a fetal size of approximately 1500 g and estimated gestational age of 29–31 weeks. There was considerable oedema present in the distal lower extremities. The remainder of the physical examination including neurological examination was unremarkable. Over the next 24 h the patient did not improve despite therapy with the addition of hydralazine to the antihypertensive regimen; the blood pressure remained 170–200/105–115 mmHg, and brisk deep tendon reflexes developed. Urinalysis showed ++ protein, platelet count dropped from 243 000/μl to 128 000/μl, and the serum transaminases were twice the normal concentrations. A diagnosis of impending eclampsia was made and the patient was delivered of a 1450 g female infant by caesarean section. No large fluctuations in the blood pressure or heart rate were noted during the operation and within 24 h of delivery the blood pressure dropped to 160/100 mmHg (Fig. 1).

On the fifth day after delivery, the patient developed a minimal frontal headache and was found to have a supine blood pressure of 235/130 mmHg with a heart rate of 115 beats/min despite continued treatment with α-methyldopa and hydralazine (Fig. 1). No significant postural changes in blood pressure or heart rate were noted, and the patient had no signs of agitation or distress and neither flushing nor diaphoresis were noted. Fundoscopic examination showed mild arteriolar narrowing but was otherwise normal. Examination of the heart revealed a rapid, regular rhythm and the presence of a fourth heart sound. No peripheral oedema was noted at this time and the neurological examination was entirely normal. Laboratory data revealed a normal urinalysis; the haematocrit was 32% (35% before delivery); the platelet count was 236 000/μl and the bleeding time was 9 min. The serum electrolytes, creatinine, transaminases, glucose, protein electrophoresis, and blood urea nitrogen were within normal limits. Electrocardiogram showed normal sinus rhythm at 120 beats/min, normal conduction, and no evidence for left ventricular hypertrophy or ischemia. The X-ray of the chest was unremarkable. A 24-h collection of urine for creatinine clearance, catecholamines, vanillylmandelic acid,

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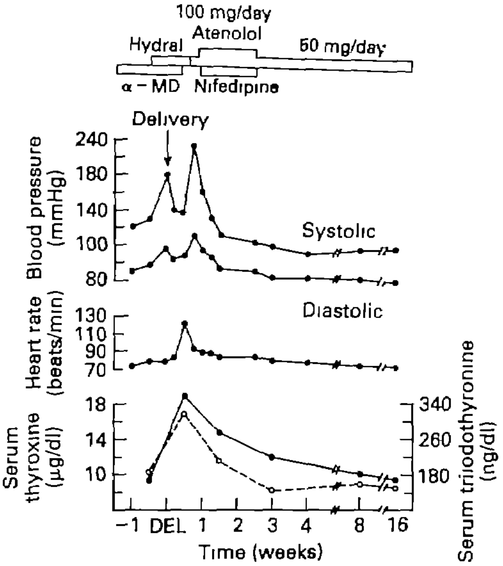

Fig. 1. Clinical course of a patient with accelerated hypertension secondary to postpartum thyrotoxicosis. The serum thyroxine (●—●) and triiodothyronine (○--○) levels are total concentrations (free + bound).

and metanephrines was normal. The thyroid function testing showed a triiodothyronine uptake ratio of 0·88 (normal, 0·89–1·16), serum thyroxine radioimmunoassay of 19 μg/dl (normal, 4·9–10·6), triiodothyronine radioimmunoassay of 315 ng/ml (normal, 75–222), free thyroxine index of 16·9 (normal, 4·5–11), and a thyroid stimulating hormone of <2 mu/l (normal, 1–6). Antithyroglobulin and antimicrosomal antibodies were absent. The thyroid hormones (thyroxine and triiodothyronine) examined from serum obtained at the initial admission were normal (Fig. 1). A thyroid uptake study performed 8 days postpartum with ^{123}I-sodium iodide demonstrated 4% uptake at 6 h and 8% at 24 h (normal, 15%–30% at 24 h). A thyroid scan showed a decreased but homogenous uptake of 5 mCi of ^{99m}Tc-pertechnetate consistent with thyroiditis.

The patient was begun on atenolol, 50 mg daily, but had no improvement in the first 2 days; subsequently she was placed on atenolol, 100 mg daily, and nifedipine, 60 mg daily, in three divided doses. There was a marked improvement in the blood pressure and heart rate levels within 3 days. Over the subsequent 3 weeks, the nifedipine was discontinued and the dose of atenolol was reduced to 50 mg daily with normalization of the blood pressure. Eight weeks after delivery the thyroid function normalized and at 16 weeks after delivery, antithyroid microsomal antibodies rose to a titre of 1:1600 antithyroglobulin antibodies remained negative; and the 24-h uptake of ^{123}I was 22%.

Discussion

The patient described was chronically hypertensive and developed superimposed pre-eclampsia, and as one might expect, blood pressure readings in the first 2 days postpartum dropped substantially. Five days postpartum, a marked rise in blood pressure accompanied by a sinus tachycardia suggested a catecholamine-mediated process, but plasma catecholamines and urinary catecholamine metabolites were not elevated. The clinical features of tachycardia, marked rise (60/25 mmHg) in blood pressure, hyperthyroxinaemia, moderately suppressed thyroid uptake of ^{123}I, and development of antithyroid antibodies described in this patient are most compatible with postpartum thyroiditis with hyperthyroidism (Amino *et al.* 1977; Ginsberg & Walfish 1977; White & Andreoli 1984; Singer & Gorsky 1985).

In two recent surveys, the prevalence of postpartum thyroid disease has been in the range of 4–7% (Amino *et al.* 1982; Jansson *et al.* 1984). Current evidence supports an underlying autoimmune cause for postpartum thyroid dysfunction (Amino *et al.* 1978) and there may be a familial tendency (Fein *et al.* 1980; Singer & Gorsky 1985). Amino *et al.* (1980) reported that both total lymphocyte counts and natural killer cell counts have been observed to decrease during pregnancy and increase after delivery, so that antibody-dependent, cell-mediated cytotoxicity may have a role in postpartum thyroiditis.

Patients with postpartum thyrotoxicosis have generally presented with fatigue, nervousness, palpitations, tremors and heat intolerance 3 days–6 weeks after delivery (Ginsberg & Walfish 1977; Singer & Gorsky 1985). Although most patients are described as having sinus tachycardia, coexisting hypertension or acceleration of pre-existing hypertension is rare (White & Andreoli 1984). Thyrotoxicosis may induce a marked increase in systolic blood pressure with a modest decrease or no change in diastolic blood pressure secondary to an increase in heart rate, cardiac index, and myocardial contractility (Amidi *et al.* 1968; Fowler 1982). Our patient showed a rise in both systolic and diastolic blood pressure concomitant with a marked elevation of the thyroid hormones (Fig. 1). It is not clear why the diastolic blood pressure rose so markedly but perhaps there was increased catecholamine receptor sensitivity secondary to hyperthyroxinaemia (Barker 1951; Brewster 1956; Coulombe *et al.* 1977) or increased vascular reactivity associated with the resolving pre-eclampsia.

The management of a patient with postpartum thyroiditis with hyperthyroidism should be directed at reduction of symptoms, heart rate and blood pressure since the clinical course is benign and the disease usually self-limiting. In most reported cases, β-adrenergic blocking agents have controlled the haemodynamic abnormalities of the thyrotoxicosis. Antithyroid medications are unnecessary and generally ineffective since in this and other forms of thyroiditis, massive amounts of thyroid hormone have been released into the circulation via leaks from cellular disruption in the gland.

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Primary Hodgkin's disease of the ovary. Case report

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Case report

A 41-year-old married Scots woman with five children had been attending the gynaecological out-patients for some years with uterovaginal prolapse. Because of her continuing obesity and reluctance to have surgery, she had been treated with a ring pessary and was seen regularly. In 1985, for the first time, she reported metrorrhagia and occasional lower abdominal discomfort. Her obesity prevented adequate clinical examination but there appeared to be a pelvic mass.

Examination under anaesthesia confirmed a pelvic mass which was considered either to be a fibroid uterus or an adnexal swelling. Diagnostic curettage produced no curettings. At laparotomy there was a moderate amount of clear ascitic fluid present and bilateral solid ovarian tumours, the left being approximately 11×8 cm in diameter and the right 5×5 cm. Each was closely adherent to the uterus and there was considerable induration of the parametrium and paracolpos. There was also a 5 cm diameter tumour within the broad ligament and involving the left tube.

Ovarian malignancy was suspected and the ovarian masses were excised together with bilateral salpingectomy, subtotal hysterectomy and subcolic omentectomy. Because of the friable and indurated nature of the paracolpos the lower portion of the cervix was left *in situ*. Exploration of the abdomen before closure showed no signs of neoplasia elsewhere. Bowel, stomach, liver, spleen and para-aortic nodes appeared normal.

Apart from suprapubic wound breakdown, convalescence was straightforward. Sternal marrow aspirate showed no abnormality, chest X-ray was normal and CAT scan was negative for other sites of Hodgkin's deposits.

Chemotherapy was decided on and the patient has been given 12 pulses at 2-week intervals of vincristine, Adriamycin, bleomycin and DTIC-Dome (Bayer).

Pathology report

Gross appearance

The subtotal hysterectomy specimen consisted of the uterus, 7 cm in length, with both adnexae attached. The left ovary measured 11 cm in its largest and 8 cm in its smallest diameter. A separate tumour, 5 cm in diameter, was present within the broad ligament and appeared to involve the tube. The right ovary was 6 cm in diameter and contained a cyst 2 cm in size.

A separate sheet of omentum measuring 24×8 cm was also included.

Histological appearance

Microscopy of both ovaries and the mass in the left broad ligament showed Hodgkin's disease containing classic binucleate Reed–Sternberg cells (Fig. 1). The specimen of omentum also contained numerous foci of Hodgkin's disease.

In addition to Reed–Sternberg cells, there was a polymorphic cell infiltrate composed of abundant abnormal reticulin cells, eosinophils and occasional plasma cells. Because of the sparsity of the lymphocyte infiltrate in areas with abundant abnormal reticulin cells a diagnosis of Hodgkin's lymphoma of lymphocyte depleted type was made using the Rye classification (Lukes & Butler, 1966).

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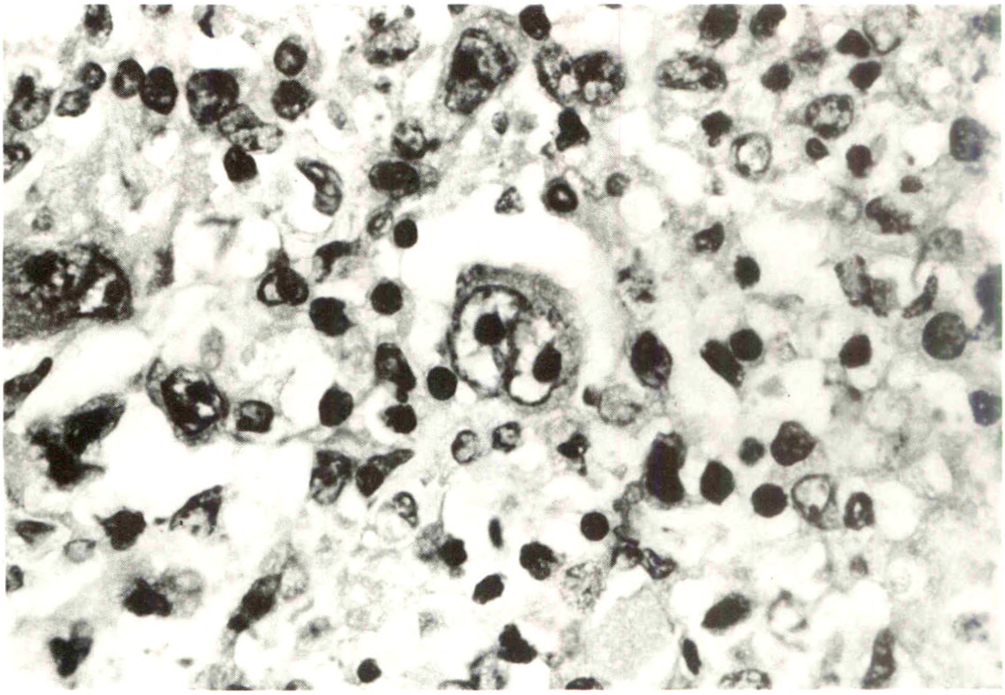

Fig. 1. Histology showed Reed–Sternberg cells. Haematoxylin and eosin ×700.

Discussion

Since Hodgkin's initial description in 1832 the classification of malignant lymphoma has undergone considerable revision, the term lymphoma first appearing in 1871.

Originally the disease entity was subclassified into giant follicular, lymphosarcoma (lymphocytic/lymphoblastic), reticulum cell sarcoma and Hodgkin's disease. The designation lymphosarcoma has been confusing since well-differentiated lymphocyte and other lymphomatous variants, regardless of all types, were included.

Currently lymphomas are divided into Hodgkin's and non Hodgkin's type depending on the cellular characteristics and pattern of growth (Rotmensch & Woodruff 1982).

The ovarian lymphoma is very rare and Hodgkin's disease of the ovary is even rarer. There seem to be no references to ovarian Hodgkin's disease before 1960 and only four cases have been reported since then.

The occurrence of Hodgkin's disease in the ovary can be attributed to the occasional presence of lymphoid tissue in the medulla or hilus of the ovary as reported by Woodruff *et al.* (1963). Lymphocytes may also arise from the primitive perivascular reticular cells and can give rise to Hodgkin's disease (Bloom & Fawcett 1965).

Diagnosis of primary ovarian Hodgkin's disease is possible only by histological confirmation following laparotomy.

As the tumour is highly radiosensitive the treatment of choice in the appropriate case is surgery followed by radiotherapy. Where there is dissemination, the disease can be treated with good prognosis by cytotoxic drug therapy following surgery, as in the present patient.

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SHORT COMMUNICATIONS

Elevation of maternal α-fetoprotein serum levels in relation to fetomaternal haemorrhage after second trimester pregnancy termination by aspirotomy

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Fetomaternal haemorrhage (FMH) after termination of pregnancy in the second trimester has been reported previously (Katz 1969; Queenan *et al.* 1971; Voigt & Britt 1969). Several authors have observed a rise in maternal serum α-fetoprotein (AFP) concentration in association with FMH (Seppälä & Ruoslahti 1972; Nørgaard Pedersen 1974; Kjessler & Johansson 1977; Los *et al.* 1979). The occurrence of an increase in maternal serum AFP after amniocentesis has also been documented (Chard *et al.* 1976; Mennuti *et al.* 1980). The discrepancy found between the results of fetal red cell count and the increased concentration of maternal serum AFP as an indicator of FMH has been attributed to a greater sensitivity of AFP changes than the Kleihauer test (Lachman *et al.* 1977). According to Dallaire *et al.* (1980), passage of amniotic fluid into the maternal circulation sometimes accounts for a rise in maternal serum AFP concentration following amniocentesis.

Patients and methods

The study included 103 patients referred to the pregnancy termination unit of the centre for Human Reproduction in Leiden. The pregnancy terminations were performed under local anaesthesia by cervical dilatation, aspiration and instrumental removal of fetal parts and placenta (aspirotomy) (Beekhuizen *et al.* 1982).

The mean gestational age at termination was 15·3 weeks (range 12–19 weeks). The duration of pregnancy was calculated from the date of the last menstrual period and confirmed by vaginal examination and inspection of fetal parts after the procedure (Birbeck 1976). In 47 patients (46%) fetal age was confirmed by ultrasound biparietal diameter measurements.

The study had the approval of the hospital ethics board and informed consent was obtained from all participants.

Maternal venous blood samples were obtained 15 min before and 15 min after the operation. Blood smears were made and treated according to a modification of the Kleihauer-Betke technique (Los *et al.* 1979). The procedure permits a clear differentiation between fetal and maternal cells by observing the stained smears with an interference microscope. In each slide 600 000 erythrocytes were scanned. The total number of fetal red cells counted was taken as the fetal cell score. The volume of FMH was estimated using the calculation presented by Los *et al.* (1979). The reproducibility of the fetal cell score at a high and at a low level is within the 90% probability of Poisson statistics. The sensitivity was four fetal cells, representing a FMH of 0·06 ml at 16 weeks gestation.

AFP measurements were carried out by the Rijksinstituut voor de Volksgezondheid (Dr A. M. Hagenaars), Bilthoven, The Netherlands, using an ELISA ('Sandwich') technique (Hagenaars *et al.* 1980). Hagenaars *et al.* (1980) reported that the values obtained by this method show a good correlation (r=0·94) with the RIA (double antibody) technique. A maternal serum AFP increase of ≥100 μg/l after pregnancy termination was considered to indicate that fetomaternal bleeding had occurred.

Results

After the operation fetal cell scores corresponding to a FMH of at least 0·1 ml were detected in

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Table 1. Frequency of fetomaternal haemorrhage (FMH) at termination of pregnancy (12–20 weeks) as determined by fetal cell counts

FMH (ml)	No. of subjects (n=103)	%
0	25	24·3
0·01–0·049	21	20·4
0·05–0·099	13	12·6
0·1 –0·49	32	31·1
0·5 –0·99	5	4·8
1·0 –3·5	7	6·8

Table 2. Increase in maternal serum alpha-fetoprotein (AFP) concentrations after termination of pregnancy between 12 and 20 weeks gestation

Rise in AFP (μg/l)	No. of subjects (n=103)	%
0	4	3·8
1–49	10	9·7
50–99	25	24·3
100–499	46	44·7
500–999	11	10·7
1000–2999	4	3·9
≥3000	3	2·9

44 patients (42·7%; Table 1). In seven patients FMH exceeded 1 ml. In only four (3·8%) of the post-abortion blood samples was there no increase in AFP concentration. In 64 of the women (60·8%), we noted an AFP increase of ≥100 μg/l (Table 2). In 25 women there was no increase in fetal red cells after pregnancy termination, but 9 (36%) of them showed a rise in AFP serum concentration of ≥100 μg/l. There was a good correlation (r=0·94) between the rise in fetal red cell score and the increase in maternal serum AFP concentration after pregnancy termination. The frequency of FMH of ≥0·1 ml increased significantly with the duration of pregnancy (χ^2 = 21·01, P<0·01; Fig. 1). This was also true for maternal AFP serum concentration rises of ≥100 μg/l (χ^2 = 22·40, P<0·01; Fig. 2).

Discussion

The risk of FMH after pregnancy termination has been reported in several studies (Katz 1969; Queenan *et al.* 1971; Voigt & Britt 1969). The high frequency of fetomaternal transfusions found in this study corresponds with the data reported by Queenan *et al.* (1971) and by Voigt & Britt (1969) for second-trimester pregnancy termination. We have also confirmed that there is a progressive increase in the frequency of FMH with gestation. A FMH of between 1 and 3·5 ml was found in 6·8%. If use is made of the 'rule of thumb' that 10 μg anti-D immunoglobulin can neutralize in 1 ml fetal blood and thereby prevent Rh (D) sensitization, a dose of 75 μg anti-D immunoglobulin should offer complete protection for Rh (D)-negative women undergoing second-trimester abortion. Increased serum AFP concentration in the maternal plasma, in general, seems to be a more sensitive indicator of FMH than the Kleihauer test. Agglutination of fetal cells in ABO incompatibility may account for a false-negative Kleihauer tests. On the other hand, when there is only a minor disruption of the fetomaternal barrier, fetal serum may pass into the maternal circulation without fetal cells and there is always the possibility that passage of amniotic fluid into the maternal circulation accounts for a risk in raised maternal serum AFP concentration.

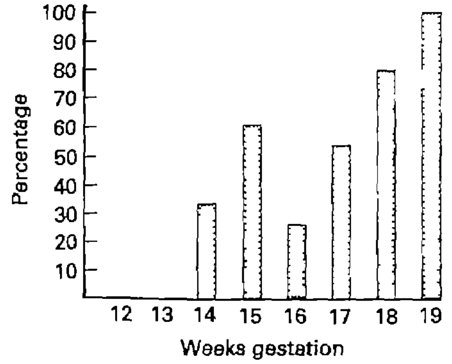

Fig. 1. Percentages of women with fetomaternal haemorrhage of ≥0·1 ml after termination of pregnancy between 12 and 20 weeks gestation.

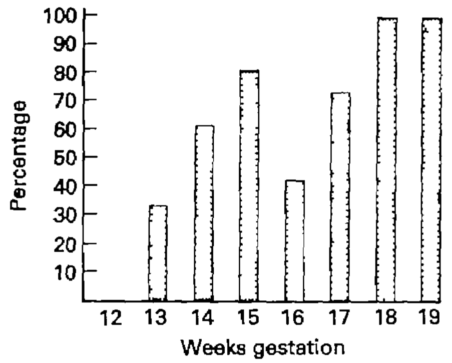

Fig. 2. Percentages of women with increases in serum α-fetoprotein of 100 μg/l after termination of pregnancy between 12 and 20 weeks gestation.

In pregnancies terminated at 16 and 17 weeks we found a dip in the frequency of FMH as indicated by either a positive Kleihauer test or a raised AFP level. We have no explanation for this unexpected result (Figs 1 and 2). Contrary to Lachman *et al.* (1977), we do not consider the maternal serum AFP rise to be useful for calculating the volume of the FMH because of the uncertainty of the fetal serum AFP concentrations.

Acknowledgments

We wish to thank the staff of the Center for Human Reproduction in Leiden for their cooperation in sample collection. We are also grateful to Dr A. M. Hagenaars (RIV, Bilthoven) for performing the AFP measurements and to Professor Dr M. J. N. C. Keirse and Dr D. O. E. Gebhardt for their kind support. Finally we would like to express our gratitude to Dr R. Brand for his statistical assistance and to Mrs J. Stam-Rietkerken for her help in preparing this manuscript.

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BOOK REVIEWS

Male Reproductive Dysfunction. Diagnosis and Management of Hypogonadism, Infertility and Impotence (Basic and Clinical Endocrinology Series Vol. 7) edited by Richard J. Santen & Ronald S. Swerdloff. Marcel Dekker Inc., New York, 1986, 646 pages with figures and tables. $99.00 (US and Canada), $119.00 (all other countries)

It was with great pleasure that I received this book to review. At long last, a well-written comprehensive textbook of andrology has arrived on the scene. This book is made up of 26 chapters in five sections which cover not only the anatomical and physiological basis of andrology, but also all the major causes of infertility in men. The authors of each chapter, who are mainly, but not exclusively American, have covered each subject in a well-balanced and most thorough way, thus making each contribution both informative and comprehensive. Each chapter is also very well-referenced.

The book begins with a section on basic andrology and includes an especially fine contribution by Alex Vermeulen on Leydig cell physiology. Included in this section is a chapter on the ontogeny of male sexual development which is a subject to which scant attention is paid in many books on andrology. Both Leydig cell and germ cell dysfunction are reviewed in a series of chapters in the second section of the book and includes the clinical as well as the pathophysiological basis of many problems seen in a male infertility clinic. Two particularly good chapters in this section review infection and also autoimmunity as a cause of male infertility but all the major causes of infertility in men are fully reviewed and these chapters devote considerable space to the management of these numerous problems.

The fourth section of this book concerns itself with the problems of psychogenic sexual dysfunction, a problem that is carefully and comprehensively reviewed. However, one glaring omission in this otherwise excellent book is that scant attention is paid to the organic causes of sexual dysfunction and there is scarcely a mention of the pharmacological treatment of neurogenic impotence. The book is completed by a review of the development of a male contraceptive.

Overall, this is an excellent postgraduate textbook of andrology. The paucity of illustrations makes it a little heavy going but the book is already made up of over 600 pages; more illustrations would increase both its size and in particular its price.

Apart from the omissions mentioned above, this book provides a comprehensive view of the whole subject of andrology in general and of male infertility in particular. It is one of the best books of its kind that have been produced for some years.

Anne M. Jequier

Litigation and Obstetrics and Gynaecology (Proceedings of the Fourteenth Study Group of the Royal College of Obstetricians and Gynaecologists), edited by G. V. P. Chamberlain, C. J. B. Orr & F. Sharp. Available in UK from the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, £15.00 (plus postage). Available outside the UK form Perinatology Press, P.O. Box 6827, Ithaca, NY 14851, USA. $55 (plus postage).

Only a very complacent practitioner in obstetrics and gynaecology could resist feeling some concern about the possibility of involvement in litigation. So important has the issue of litigation become that it was the chosen subject for the Fourteenth Study Group of the Royal College of Obstetricians and Gynaecologists. Represenitves of the Fellows and Members of the College and of the three Defence Societies (The Medical Defence Union, Medical Protection Society and Medical and Dental Defence Union of Scotland) were invited to discuss areas of mutual interest and, as usual, the Proceedings of the Study Group have been published in book form. The President of the College introduces the subject in the opening chapter, highlighting the profound change in the relation between the profession and the public over the past century and noting society's increased demands from medicine. There is much ignorance of the process of litigation so the chapter which examines the anatomy and physiology of a claim is also valuable by way of introduction. Then there are contributions which consider the effects of resources on claims, problems of prescribing in obstetrics and anaesthesia, regional and general. The major part of the volume comprises paired presentations which examine, in turn, the clinical and medico-legal aspects of areas which seem to have the greatest potential for producing litigation. These are accidents in gynaecclogical surgery, therapeutic abortion, contraception, sterilization, genetic testing and antenatal testing for congenital abnormality, fetal hypoxia, operative delivery, natural childbirth and home deliveries. Also, there is a strategically placed contribution from a New Zealand lawyer on the state-funded system of no-fault compensation for personal injury by accident, which recognizes the need for financial assistance for the victims of medical mishaps, whether or not there has been negligence. Each chapter, or pair of chapters, is followed by a discussion of the subject by the participants, chaired either by the president of the College or presidents of the Defence Societies. These discussions are quite frank and, in some areas, demonstrate the differing views of two or more respectable bodies of medical opinion. It is fascinating to speculate about the factors which either promote or discourage litigation. For example it is noted that few claims arise from treatment involving radical pelvic surgery for malignant disease which may suggest that the training of these gynaecologists is such that fewer avoidable complications occur, or that the patient realizes the significance of the surgery and is grateful whatever the outcome. It is also noted that there are more claims arising from complications of spontaneous than from therapeutic abortion, giving rise to suspicion that there is a degree of reluctance to bring an action which might involve public embarrassment. Perhaps the same explanation applies to the paucity of actions for impaired sexual function after over-enthusiastic vaginal repair surgery.

It should be a consoling reminder that it is doctors, not lawyers, who set the standards in medical negligence cases: the legal test is whether a doctor has failed to act in accordance with the practice accepted at the time as proper by a responsible body of medical opinion. The crucial importance of adequate written records is emphasized again and again in contributors' texts and discussions. In mounting a defence, probably years after the event, it is useless claiming that an appropriate action was taken if the records do not show it.

The book has been published promptly and economically and the occasional misplaced table and references do not detract from the value of the experience and wisdom of the contributors. All doctors working in obstetrics and gynaecology, as trainees or specialists, will benefit from reading it and find it a valuable addition to their personal bookshelf.

R. P. Husemeyer

Infertility. Male and Female edited by Vaclav Insler & Bruno Lunenfeld, Churchill Livingstone, Edinburgh, 1986, 740 pages with figures and tables, £70.00

There should be an assured future for a book which brings together 47 world experts in the fields of reproductive anatomy and physiology and male and female fertility to provide critical reviews of the science and clinical aspects of infertility. There is a clear need for such a work as the basic text for the newly emerging subspeciality. The list of authors is impressive and the stated aims of the editors are commendable including as they do the 'couple approach'.

There are a number of excellent chapters where the results of treatment options are assessed critically and clear recommendations are given for practical management regimens. Notable among these are the chapters on gonadotrophins (Brown), surgery in the female (Winston & Nargara) and drug treatment in the male (Schill). Other sections are less satisfactory.

The scientific chapters are patchy in terms of readability and interest. Some of the clinical chapters lack a sense of proportion detailing impossibly elaborate investigative regimens and others list plans of treatment with little attempt to establish their real worth. Any editor of a 1986 infertility text should have insisted on treatment pregnancy rates being quoted in such a way as to allow proper comparison with other treatments or no treatment. Statements such as 'six out of thirty-two became pregnant' without reference to length of treatment or other infertility factors have confused the infertility literature for too long, but are unfortunately still found in this book.

One author defends the unproven technique of A.I.H. with multiple stored ejaculates thus: 'The success rate of this treatment may be very low in relative terms of patient numbers, but it is actually 100% in terms of happiness and fulfilment for those fortunate successful patients'.

The editors have let through an unusual number of mistakes in spelling, table and figure presentation, and have also allowed significant overlaps and sometimes contraditions between chapters. These shortcomings do not altogether spoil the book, but they turn what might have been a really great work into one which is merely good in parts.

David Joyce

Te Linde's Operative Gynecology sixth edition edited by R. F. Mattingly & John D. Thompson. J. P. Lippincott Company, Philadelphia, 1985, 938 pages with figures and tables, £98.00

It was with a sense of history that I read and reviewed this book. It is a major American textbook on gynaecological surgery, stemming directly from the famous school of gynaecology led by Howard A. Kelly at Johns Hopkins Hospital, Baltimore and was originally written by his pupil, Richard Te Linde (who is still living). Authorship then passed to his pupils, Richard Mattingly and John Thompson. I also read it with humility, as this book has been a significant influence on the training of American residents in gynaecological surgery. With its editors directly descended from one school, is it open to the charge of parochialism? I think not—the calibre and stature of its editors and contributors and their presentation of critical literature reviews avoids this. It is in its sixth edition and tragically Richard Mattingly, friend and mentor, died prematurely, some three months after its publication.

This is more than a simple textbook of operative gynaecology, as its title might imply. Its strength lies in its detailed coverage of epidemiology, pathology, clinical presentation and operative surgery, spanning a full list of surgical topics. Where appropriate and relevant to either pathology or treatment, a critical review is presented of the state of the art and current literature, followed by the author's viewpoint. Although American in style and referencing, it nevertheless presents an international, up-to-date and acceptable standard of surgery from which we can learn much with perhaps only a few deviations from standard UK practice. It is well illustrated, although not as profusely as some texts. The majority of illustrations are half-tone and it is a delight to find that the original Max Brödel drawings (although occasionally altered) are included and are still amongst the finest examples of medical illustration.

The authors recognize and welcome the arrival of sub-specialization and many specialist contributors have been invited to write chapters, so that the book presents a wide range of surgical expertise.

The first section includes an excellent review of the history of European and American contributions to pelvic surgery which gives perspective to this work. Professional liability is an early chapter and one benefit resulting from the horrendous increase and toll of medical litigation in the United States has been the introduction of close scrutiny by peer review committees of the indications for various surgical procedures, especially hysterectomy. Perhaps the pendulum has swung too far, when the author of a later chapter on hysterectomy recommends a second opinion before any hysterectomy. A clear account of relevant pelvic anatomy is given here, although perhaps an undue emphasis is devoted to pelvic collateral circulations.

The second section deals with topics often neglected in our own training—pre- and post-operative care (particularly dealing with the elderly), parenteral nutrition and electrolyte metabolism: it correctly emphasized the importance of pre-operative identification of the high-risk patient and of her management.

The remaining two sections of the traditional views of non-neoplastic conditions and a neoplastic section, which with a minor digression into benign vulvo-vaginal topics, is up-to-date and didactic.

My criticisms are few: I would have liked all textual references to be included in the reference list and in the chapter on pelvic inflammatory disease, more emphasis is needed on chlamydial infection rather than on tuberculosis. A Lewis cystometer is still recommended for urodynamic assessment. I would have liked more coverage on laser surgery and methods of oocyte recovery.

It would be difficult to find a better textbook on general gynaecology and operative surgery and its size is one reason for its cost. If we are to develop and model our surgery on the best of international standards, all trainees ought to read this book and consultants would find much in this to refresh and refurbish their techniques I commend it.

Stuart L. Stanton

Books received some of which may be reviewed at a later date

Drug and Chemical Action in Pregnancy: Pharmacologic and Toxicologic Principles (Reproductive Medicine Series, Volume 8) edited by Sergio Fabro & Anthony R Scialli. Marcel Dekker Inc., New York, 1986, 544 pages illustrated, $87.75 (US and Canada), $107.50 (all other countries)

Ovulation Induction and In Vitro Fertilization by Josef Blankstein, Shlomo Mashiach & Bruno Lunenfeld. Year Book Medical Publishers Inc., Chicago, 1986, 212 pages with figures and tables, £29.00

Quantitative Obstetrical Ultrasonography edited by R. L. Deter, R. B. Harris, J. C. Birnholz & F. P. Hadlock. John Wiley & Sons, New York, Chichester, 1986, 377 pages with figures and tables, £43.25

Drug Use in Pregnancy: Mother and Child edited by Ira J. Chasnoff. MTP Press Ltd, Lancaster, 1986, 163 pages with figures and tables, £30.00

Ultrasound Annual 1986 edited by Roger C. Sanders & Michael C. Hill. Raven Press, New York, 1986, 279 pages with figures and tables, $87.00

Perinatal Medicine—Problems and Controversies edited by G. C. Di Renzo & D. F. Hawkins. Cortina International, Verona, distributed by Raven Press, New York, 1986, 221 pages with figures and tables, $47.00 (approx £30).

Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates Fourth Edition edited by C. R. Whitfield. Blackwell Scientific Publications, Oxford, 1986, 818 pages with figures and tables, £65.00

Reproductive Endocrinology: Physiology, Pathophysiology and Clinical Management Second Edition edited by Samuel S. C. Yen & Robert B. Jaffe. Holt Saunders Ltd, Eastbourne, 1986, 806 pages with figures and tables, £88.00

Care of the High-Risk Neonate Third Edition edited by Marshall H. Klaus & Avroy A. Fanaroff. Holt Saunders Ltd, Eastbourne, 1986, 455 pages with figures and tables, £19.50

Basic Science in Obstetrics and Gynaecology—A Textbook for MRCOG Part 1 Edited by Sir John Dewhurst, Michael de Swiet & Geoffrey V. P. Chamberlain. Churchill Livingstone, Edinburgh, 1986, 256 pages with figures and tables, £15.00

Proceedings and Symposiums

Endocrine Therapy of Breast Cancer (International Workshop on Experimental and Clinical Endocrine Therapy of Breast Cancer held at Bad Schauenburg/Liestal, September, 1985) edited by U. Eppenberger, D. Fabbro & P. Schafer. Karger, Basel, 1986, 96 pages with figures and tables, SwFr 50, DM 60, US$28.00

WHO Expert Committee on Venereal Diseases and Treponematoses Sixth Report (Technical Report Series No. 736) World Health Organization, Geneva, 1986, 141 pages with figures and tables, SwFr 18, US$9.00

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Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc. Tables are not included in this classification and should *not* be submitted as photographs. Original X-ray films should not be sent—glossy prints must be submitted.

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column).

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The identity of patients in illustrations should be concealed by masking the face or eyes, or written permission for publication from the patient or the parent or guardian must be supplied.

Units and abbreviations

Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg). If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors. Standard abbreviations, without punctuation, are used. *Units, Symbols and Abbreviations* (1977) published by the Royal Society of Medicine provides a useful guide. Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both summary and text, followed by the abbreviation in parenthesis.

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

Statistics

Authors should describe clearly the design of their investigation and the source of the data. All statistical methods should be specified so that it is clear which was used where. Papers omitting this information may be returned without review. The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else.

Some points of detail to note are:

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic.
(2) The use of confidence intervals is encouraged.
(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean . . . was 14·2 (SD 3·2) mg' is preferred.
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
(5) Unusual methods of analysis should be described and/or referenced.

Authors are referred to the general statistical guidelines of Altman *et al.* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

Human experiments

Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work. The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References

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Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows:

Name(s) and initials of all author(s), year of publication (in brackets), title of the article, name of the journal (abbreviated according to *Index Medicus*), volume number, first and last page numbers. In the case of books the order is: Name(s) and initials of author(s), year of publication (in brackets), full title, edition, publisher and place of publisher, page numbers. Where appropriate, the chapter title and the names of the editors should be given.

References to 'personal communications' and 'unpublished work' may be quoted in the text but should not be included in the references. Examples of the style to be used are given below.

Trudinger, B. J., Lewis, P. J. & Petit, B. (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86**, 432–436.

Hytten, F. E. & Leitch, I. (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p. 26.

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Manuscripts should specify the name and address of the author to whom correspondence and page proofs should be sent. Only essential corrections can be accepted, more extensive alterations, which may delay publication, will be charged to the author. Fifty offprints of each paper are supplied free, but additional copies may be ordered on the printed card sent with the proofs.

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